Evaluation of the impact of BMI and P_4/E_2 ratio at the day of HCG on ICSI outcome

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Abstract: Aim: to evaluate the impact of BMI and progesterone/estradiol (P_4/E_2) ratio at the day of HCG triggering on ICSI. **Method:** Prospective observational study conducted at the Assisted Reproductive Unit, International Islamic Center for population studies and research during the period from November 2016 to August 2017. A total of 200 infertile women were recruited and subjected to ICSI using the standard long GnRH-agonist protocol. P_4/E_2 ratio was correlated to the pregnancy rate in all the included patients then they were classified into two groups according to their BMI Group I: included 100 infertile women with BMI 25≤30 kg/m2. Group II: included100 infertile women with BMI 30≤35 kg/m2. Different outcome parameters were compared between the two groups including peak estradiol and progesterone levels on day of HCG, P_4/E_2 ratio, in addition to the number of retrieved oocytes, their maturity, fertilization rate, number of grade A embryos and the pregnancy rate. **Results:** Females having low progesterone/ estradiol ratio (≤0.38) were able to achieve a higher chemical pregnancy rate. These females also had significantly high number of oocytes retrieved and number of grade A embryos. **Conclusion:** P_4/E_2 ratio <0.38 may be a good prognostic factor for chemical pregnancy rate in ICSI cycles, however BMI cannot be regarded as a predictive factor for chemical pregnancy and this was applied for overweight and obese patients.
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Key Words: P_4/E2 ratio, ICSI, BMI.

1. Introduction

Obesity also plays a significant role in reproductive disorders, particularly in women. It is associated with anovulation, menstrual disorders, infertility, difficulties in assisted reproduction, miscarriage, and adverse pregnancy outcomes *(Dağ and Dilbaz, 2015).* Premature luteinization (PL) which is usually defined as a subtle, premature rise in serum progesterone (P_4) concentrations on or before the day of human chorionic gonadotropin (HCG) administration remains one of the most controversial issues in modern reproductive endocrinology *(Fanchin et al., 1997; Shulman et al., 1996).* Most studies used an absolute P_4 level on the day of HCG administration as an indicator of PL, and the cutoff level differed from 0.8 to 2 ng/mL *(Cedars et al., 1990; Givens et al., 1994; Yovel et al., 1995; Copperman et al., 1996).*

Younis et al (1998) claimed that P_4/E_2 ratio was more accurate to detect low ovarian reserve and less oocyte were retrieved on OPU. Other studies showed that elevation in P_4/E_2 ratio revealed higher oocytes collection and didn't harm the pregnancy rates in normo-ovulatory patients. P_4/E_2 ratio has been suggested as a marker for predicting clinical pregnancy rates, but the evidence is conflicting *(Lai TH, et al, 2009).*

Our study assess the impact of BMI and P_4/E_2 ratio at the day of HCG triggering in infertile women undergoing ICSI treatment cycle.

2. Patients and Methods:

This is a prospective observational study conducted at the Assisted Reproductive Unit, International Islamic Center for population studies and research. AL-Azhar University cairo, egypt during the period from November 2016 to August 2017. A total of 200 infertile women were recruited and subjected to ICSI using the standard long GnRH-agonist protocol. Approval was obtained from the ethics committee of the unit The infertile women were classified into two groups according to their BMI: Group I: included 100 infertile women with BMI 25≤30 kg/m^2 (Overweight).

Group II: included 100 infertile women with BMI 30≤35 kg/m^2 (Obese).

Inclusion criteria: age ranges from 25-35 years old, BMI ranges from 25kg/m² and < 35 kg/m², good ovarian reserve as estimated by AFC more than five follicle per ovary and FSH level that below 10 mIU/L, no evidence of uterine pathology, patients undergoing ICSI using the standard long GnRH-agonist protocol.

Patients were stimulated according to the long GnRH-agonist protocol as follows: Long GnRH - agonist protocol started in the mid-luteal phase, (Day 21 of the previous cycle), by daily subcutaneous

injections with triptoreline acetate (Decapeptyl0.1 mg). until HCG administration. When serum E_2 <50pg/ml, (approximately 9-11 days after down regulation) controlled ovarian hyperstimulation was started with dose 2-4 ampoule On day 2 of the next cycle (HMG 75 IU/amp). Adjusted according the age and BMI. Then the dose was adjusted according to the ovarian response either by step up or step down detected by folliculometry.

Transvaginal ultrasound was started on day 6 of stimulation and repeated every other day till the moment when more three leading follicle reach ≥ 18 mm in diameter. The size and number of growing follicles were accurately registered in the patient's sheet. When the largest follicle reached a diameter of ≥18 mm, HMG and Decapeptyl were discontinued and 10.0001U of HCG was administered by deep intramuscular injection. Serum progesterone and estradiol levels were measured on the day of HCG administration and then progesterone/ estradiol ratio was calculated. Transvaginal ultrasound–directed oocyte retrieval was performed 36 h -

After triggering by HCG under general anesthesia.

Embryo transfer was done on day 3 from the ovum pick up day using a soft catheter. Luteal phase support was given to the patients in the form of daily 100mg progesterone in oil intramuscular injection for 14 days, and occurrence of chemical pregnancy was confirmed by evaluation of B-HCG values exceeding 50IU/liter.

Primary outcome.

Total number of oocytes retrieved, number of mature oocytes, rate of fertilization and number of grade A embryos in each group.

Secondary outcome.

To detect if the P_4/E_2 ratio has an impact on the pregnancy rate and to compare its significance between the two study groups.

Statistical analysis.

Data were statistically described in terms of range, mean ± standard deviation (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test with posthoc multiple 2-group comparisons. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant.

3. Result

In table (**1**) Mean BMI was 26.40±1.13 in group I and 32.61 ± 1.72 kg/m2 in group (II) (p < 0.001).

Table (1): Patient's characteristics.

Variable	Group I BMI [25- <30]) (N=100)	Group II BMI [30-<35] (N=100)	t-test	p-value
Age (years)	29.61±3.31	29.34±3.43	0.321	0.571
Weight (kg)	63.96±7.37	79.88±5.69	292.561	<0.001
Height (cm)	1.56±0.07	1.57±0.06	0.235	0.628
BMI	26.40±1.13	32.61±1.72	99.443	<0.001
Duration of infertility (years)	5.21±2.28	5.01±1.93	0.450	0.503
Type of infertility Primary Secondary	 80 (80%) 20 (20%)	 89 (89%) 11 (11%)	0.482	0.312

In table (2) Our results revealed the number of days of stimulation by HMG showed statistically significant difference between group I and group II (13.12 ± 1.55 days & 13.92 ± 1.96 days respectively) (p= 0.002). The number of ampoules used for ovarian stimulation also showed statistically significant difference between group I and group II (33.18 ± 9.44 & 41.87 ± 13.47 respectively) (p< 0.001). Analysis of our data revealed significant lower levels of peak estradiol and progesterone in group II patients with more decrease in estradiol levels than that observed with progesterone. There was no significant difference of P_4/E_2 ratio in both groups *(p value = 0.348)*. The P_4/E_2 ratio calculation was performed as follows: P (ng/mL) × 1,000/E2 (pg/mL).

Table (2): Duration of stimulation, number of ampoules, E_2 and P_4 in both groups.

Variable	Group I BMI [25≤30] (N=100)	Group II BMI [30≤35] (N=100)	t-test	p-value
Duration of stimulation days	13.12±1.55	13.92±1.96	10.287	0.002
Number of ampoules used	33.18±9.44	41.87±13.47	27.906	<0.001
E_2 at day of HCG (pg/mL)	3263.00±1118.22	2892.11±888.80	6.742	0.010
P_4 at day of HCG (ng/mL)	1.04±0.59	0.91±0.39	2.622	0.043
P_4/E_2 ratio	0.34±0.18	0.36±0.14	0.885	0.348

In table no (3) there is statistically significant difference among both groups regarding the number of grade A embryos and number of cryopreserved embryos.

Table (3): Primary outcome in studied cases.

Variable	Group I BMI [25≤30] (N=100)	Group II BMI [30≤35] (N=100)	t-test	p-value
Number of oocytes retrieved	8.68±1.91	9.10±2.59	1.707	0.193
Number of mature oocytes	5.96±2.03	5.63±1.79	1.487	0.224
Number of fertilized oocytes	5.12±2.14	4.92±1.84	1.503	0.217
Fertilization rate	86%	81%	2.734	0.421
Endometrial thickness at day of HCG (mm)	11.00±1.88	11.14±2.37	0.214	0.644
Number of embryos available for ET	4.95±1.82	4.88±1.56	1.203	0.245
Number of grade A embryos	4.46±1.64	2.68±1.01	9.425	0.010
Number of transferred embryos	2.43±0.66	2.35±0.59	0.820	0.366
Number of cryopreserved embryos	0.96±0.57	0.46±0.19	6.745	0.030

Table (4): Chemical pregnancy rate in both groups.

	Group I BMI [25≤30] (N=100)	Group II BMI [30≤35] (N=100)	t-test	p-value
Chemical pregnancy rate	42 (42%)	39 (39%)	0.081	0.776

In table no (4) The chemical pregnancy rate was comparable among both BMI groups.

According to receiver operating characteristic curve (ROC) analysis, the P_4/E_2 ratio which can predict chemical pregnancy rate was found to be = 0.38, AUC = 0.575, and 95 % Confidence Interval 0.489-0.748 with sensitivity of 64.8 %; specificity of 49.11 %; and overall accuracy of 58.1 %.

Area under the Curve (AUC) representing the discrimination capacity of the variable.

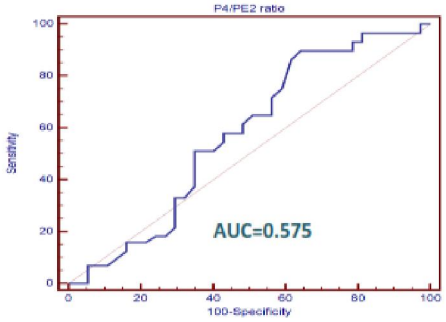

Figure (1): ROC curve for P_4/E_2 ratio to predict chemical pregnancy rate.

Table (5): P_4/E_2 ratio under the curve and p value.

Test variable	AUC	95% CI for AUC	P value
P_4/E_2 ratio	0.575	0.489-0.748	<0.001 HS

Table (6): P_4/E_2 ratio: PPV=Positive Predictive Value, NPV= Negative Predictive Value and Accuracy.

Cut-off point	Sensitivity	Specificity	PPV	NPV	Accuracy
≤0.38	64.8%	49.11%	50.2%	64.3%	58.1%

In table no (7) There is statistically significant difference between both groups regarding duration of stimulation, number of ampoules, E2 and P_4 levels at day of HCG, number of oocytes retrieved and number of grade A embryos.

Table (7): Comparison between the estimated P_4/E_2 ratios regarding stimulated cycle outcome data

Variable	P_4/E_2≤0.38 (N=120)	P_4/E_2>0.38 (N=80)	t-test	p-value
Duration of stimulation days	12.43±1.96	13.65±1.54	-2.831	0.041
Number of ampoules	35.40±11.65	40.71±12.86	-3.030	0.003
E2-day of HCG (pg/mL)	3475.67±929.36	2480.39±860.87	7.639	<0.001
P4-day of HCG (ng/mL)	0.83±0.32	1.29±0.60	-6.973	<0.001
Number of oocytes retrieved	9.66±2.07	7.74±2.09	6.406	<0.001
Fertilization rate	83%	84%	-0.424	0.672
Number of grade A embryos	4.14±1.52	3.15±1.01	5.119	<0.001
Number of cryopreserved embryos	0.71±1.34	0.64±1.21	0.878	0.381

Table (1): Chemical pregnancy rate according to the estimated P_4/E_2 ratio.

	$P_4/E_2 \leq 0.38$ (N=120)	$P_4/E_2 > 0.38$ (N=80)	X2	p-value
Chemical pregnancy rate	54 (45.0%)	27 (33.8%)	2.055	0.042

In Table (9): P_4/E_2 ratio was the significant variable in predicting chemical pregnancy.

Table (9): Logistic regression analysis of the studied variables to predict chemical pregnancy.

Variable*	Odds ratio (95% confidence)	P value
BMI	0.989 (0.912-1.073)	0.797
P_4/E_2	6.849 (1.115-42.061)	0.038

4. Discussion

There is statistically significant difference between obese and overweight patients, as total duration of stimulation was higher in the obese group than the overweight group (p= 0.002), The number of ampoules used for ovarian stimulation also showed statistically significant difference between obese and overweight patients (p< 0.001), (Table 2).

This comes in agreement With the results obtained by *Özgün* who included a prospective study of 604 women undergoing ICSI-ET. Patients were classified into five groups according to their BMI: Group A (<18.5 kg/m2), Group B (18.5 to 24.9 kg/m2), Group C (25 and 29.9 kg/m2), Group D (30 to 35.9 kg/m2), Group E (≥36 kg/m2). The total FSH dose was significantly higher in Group E compared with those women in Groups A, B, C *(Özgün et al.2009).*

Vilarino et al contradicts with our results who carried out a retrospective analysis of the results of 208 patients and found out that there is no difference in FSH requirements in obese patients compared to the normal weight women during controlled ovarian stimulation *(Vilarino et al. 2010)*.

Also our results revealed absence of significant difference among the two groups with regard to the number of retrieved oocytes, number of mature oocytes, the number of fertilized oocytes and number of embryos transferred (Table 3).

The same results about the number of oocytes retrieved also were obtained by *Luna et al. 2007, Bellver et al. 2009 and Sathya et al. 2010* in their studies.

On the contrary, *Gibbons et al* from his study which was carried out on 1,096 women under the age of forty and were clustered into two groups according to their BMI < 30 & > 30, retrospective analysis of his study revealed that the average number of eggs retrieved was significantly higher in the group with increased BMI *(Gibbons, 2006).*

*Jungheim et al*results obtained by analysis of morbidly obese (BMI >40 kg/m2) women with PCOS undergoing IVF at an American clinic has found a significant fewer oocytes collected and impaired fertilization rates, suggesting impaired follicular response and oocyte development in the morbidly obese women *(Jungheim et al. 2009).*

Our study showed that BMI was negatively correlated with number of good quality embryos and number of cryopreserved embryos. There is statiscally significant difference between overweight and obese patients, as number of good quality embryos was higher in overweight patients than obese patients (p=0.010) and number of cryopreserved embryos was higher in overweight patients than obese patients (p=0.030), (Table3).

Metwally et al suggested that young women who are obese have less chance than overweight women of having good quality embryo and cryopreserved embryos and may need a higher dose of gonadotrophins to compensate *(Metwally et al, 2007).*

On the contrary *Bellver et al* who carried out the largest single center study (6500 IVF cycles) came out with results that show that there is no difference in embryo quality and cryopreserved embryos in obese patients compared to the normal weight women during controlled ovarian stimulation and the need for higher doses of stimulation drugs among the study groups *(Bellver et al. 2009)*.

Our results revealed no statistical significant difference among overweigh and obese patients with regard to the chemical pregnancy rate which was 42% in overweight patients and 39% in obese patients (Table 4).

We conducted a multiple logistic regression analysis and effects of variables to predict chemical pregnancy. BMI failed to predict chemical pregnancy (odds ratio with its 95% confidence interval was 0.989 (0.912-1.073) & p=0.797) (Table 5).

Our results are in agreement with those of *Fedorcsak et al. 2000, Frattarelli and Kodama, 2004, Dokras et al. 2006, Luna et al. 2006, Sathya et al. 2010 and Vilarino et al. 2010* as they all came out with a conclusion that there is no statistically significant difference in pregnancy rate among the different BMI groups that was studied.

In our study ROC analysis established a cutoff value predicting a threshold which can predict

pregnancy rate. We demonstrated that a P_4/E_2 ratio with a cutoff ≤0.38 was a predictive for chemical pregnancy, AUC = 0.575, and 95 % Confidence Interval 0.489-0.748 with sensitivity of 64.8 %; specificity of 49.11 %; and overall accuracy of 58.1 % (Tables 5,6).

Elgindy et al. suggested a cutoff of 0.55 to predict clinical pregnancy in agonist cycles. Others suggested cut-offs of P_4/E_2<0.48 to achieve higher pregnancy rate. There is statiscally significant difference between high (>0.38) and low P_4/E_2, as duration of stimulation (p= 0.041), number of HMG ampoules (p= 0.003) and P_4-day of HCG (p<0.001)., E_2-day of HCG (p<0.001), number of oocytes retrieved (p<0.001), and number of grade A embryos (p<0.001) (Table 7).

Our results are in agreement with *Yuan et al* who carried a retrospective analysis involved 7451 infertile women who received the first cycle of IVF/ICSI following an extended GnRH-a protocol in patients with normal ovarian response and revealed that patients with P_4/E_2< 0.25 on the day of hCG administration were associated with low gonadotropin dosage, low progesterone level, high estradiol level, more oocytes retrieved and high-quality embryos (*Yuan et al, 2017)*.

On the contrary *O zcakir, et al* who studied the results of two-hundred and forty-eight. The patients were separated into two groups according to P_4/E_2 ratios on human chorionic gonadotropin administration day. Group A consisted of the patients whose P_4/E_2 ratio was 1 and Group B consisted of the patients with premature luteinization of which P_4/E_2 ratio was >1. Their results revealed lower number of oocytes retrieved, lower fertilization rate and lower pregnancy rate in the group with P_4/E_2 ratio more than 1*(Ozcakir et al, 2004)*.

In our study, P_4/E_2 ratio ≤0.38 was found to be associated with a significantly higher pregnancy rate compared to those having value >0.38 (p=0.042) (Table 8).

We conducted amultiple logistic regression analysis of factors influencing pregnancy rate (Table 9). P_4/E_2 ratio significantly predicted pregnancy rate (odds ratio with its 95% confidence interval was 6.849 (1.115-42.061) & p=0.038).

Our results meet with the data obtained by *singh et al* who carried a retrospective analysis involved 544infertile women undergoing fresh IVF/ICSI cycles (539 cycles) with long agonist protocol. The overall cut-off value of P_4/E_2 ratio detrimental for pregnancy was found to be ≥0.35 and found P_4/E_2 ratio is a significant predictor for pregnancy outcome without affecting fertilization rate while serum estradiol levels do not seem to affect pregnancy rate *(Singh et al, 2015).*

On the contrary, *Yuan et al* concluded that a P_4/E_2 < 0.25 on the day of hCG administration correlates with adverse pregnancy outcomes in extended IVF/ICSI treatment in patients with normal ovarian response *(Yuan et al, 2017).*

Amal et al who studied the significance of P_4/E_2 ratio on the outcome of ICSI cycles and if this relation would differ in obese vs. non-obese patients and observed that P_4/E_2 ratio cannot be regarded as a predictive factor for the ICSI outcome and this can be applied for obese and non-obese patients who showed near results of pregnancy rate *(Amal et al, 2012*).

We conclude *BMI* cannot be regarded as a predictive factor for chemical pregnancy and this was applied for overweight and obese patients. P_4/E_2 ratio <0.38 may be a good prognostic factor for chemical pregnancy rate in ICSI cycles.

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