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RESEARCH ARTICLE

EFFECT OF PRE-TREATMENT PRIOR TO ANTAGONIST REGIMEN ON CLINICAL OUTCOME OF EXPECTED POOR OVARIAN RESERVES PATIENTS USING POSEIDON CRITERIA

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ABSTRACT

PURPOSE: The study is aimed to analyse the effect of different pre-treatments on the IVF outcome of expected poor ovarian responders patients according to POSEIDON criteria. **Method**: Retrospective analysis of 364 cycles of expected POR patients who had IVF-ET from jan18 to jan20. Pre-treatment was given prior to gonadotrophins stimulation. The cycle were divided into OCP group A (N=167), estradiol valerate group B (N=56), no pre-treatment group C, (N= 141). **Result:** Demographic profile and controlled ovarian stimulation were nearly same for all POR patients where antagonist protocol was used with recombinant HCG for trigger and progesterone supplement in luteal phase. The Implantation rate was higher in Group A (26.2%) and in Group B (26.8%) as compared in Group C 14.5% (p 0.001).The clinical pregnancy was higher in Group A 36.1% and in Group B 42% as compared to Group C 21.2% (p 0.001). The abortion rate was lowest in Group A 11.4% as compared to 28.6% in Group B and 35.5% in Group C. Although biochemical pregnancy rate was lowest in Group B 19.6% as compared to Group A 31.1% and in Group C 34.0%. **Conclusion**: Pre-treatment prior to GnRh antagonist regimen in expected POR patient with OCP or estradiol valerate in luteal phase can improve clinical pregnancy outcome of POR patients. Estradiol valerate seems to be more effective than OCP. Although it may be associated with longer stimulation and higher gonadotropin consumption.

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INTRODUCTION

Recent advance in the definition and classification of expected poor ovarian responders (POR) are expected to enable clinical research and experience in a more homogenous population. However, there are few clinical studies on the expected low response population of the new POSEIDON, on and there are not many experience on how to improve the clinical outcome.
The POSEIDON criteria propose a shift of terminology of POR (poor ovarian response) to the concept of low prognosis in ART owing to decreased number of oocytes, which limits number of genetically normal embryos of transfer and affecting cumulative live birth rates (9) POSEIDON (patient oriented strategies encompassing individualized oocyte number). Low prognosis patient are in '4' groups according to the result of ovarian reserve markers (AMH, AFC, or both) female age and number of oocytes retrieved in conventional ovarian stimulation. Both oral contraceptive pills (OCPs) and estradiol valerate (E2) have been used to schedule a gonadotropin-releasing hormone antagonist in vitro fertilization (IVF) cycles (3,4,7). Since the suppression of follicle-stimulating hormone by OCPs can stay 5-7 days after stopping the pills, it seems that starting the gonadotropin-

releasing hormone (GnRH) after 6 days of pre-treatment discontinuation may be important in IVF outcomes (5). Estradiol valerate (E2) is given for 8-10 days, from day 21 till commencement of menses.as it is given for short duration its does not much suppress women own hormone production (6,8)

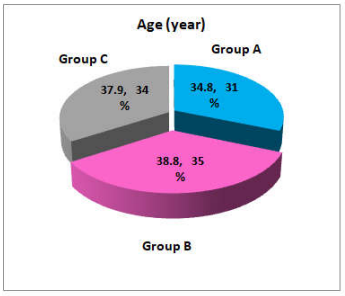
AIMS & OBJECTIVES: The study is aimed to analyse the effect of different pre-treatments on the IVF outcome at expected POR (poor ovarian responders) patients according to POSEIDON, criteria.

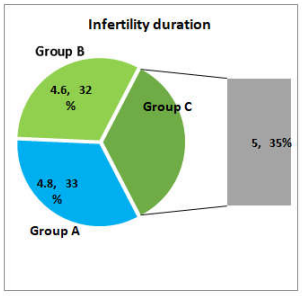
METERIALS AND METHODS

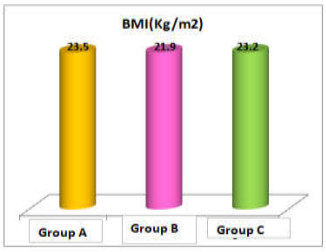
It is a retrospective analysis of 364 cycles of expected POR patient who had undergone IVF-ET in 2yr from jan 18 to jan 20 according to the pre-treatment prior to gonadotrophins stimulation, the cycle were divided into OCP (oral contraceptive) group A (N=167), estradiol vale rate group B (N=56),no pre-treatment group C, (N= 141). The clinical data, ovarian stimulation indexes, laboratory data and clinical pregnancy rates were compared among the three groups. In all cases antagonist protocol with IVF+ICSI was performed with progesterone support in luteal phase. Here OCP (E+P) was given from D3-4 of previous cycle for 21d in group A. In group B the estradiol valvate (2mg) twice daily was given from day 20 of periods in luteal phase till the next cycle commences. In group C, no supplement was given in pre-treatment cycle. These pre-treatments suppress the woman's own hormone production.

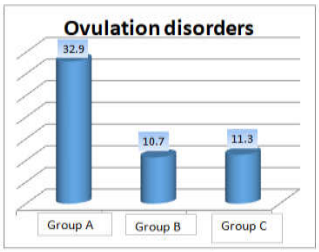
STATISTILAL ANALYSIS (characteristic of patients):
Retrospectively on analysing 2yrs data on POR patient we found the demographic profile as in group A (OCP N=167), group B (E_2N=56), group C (none N=141) under categories of age infertility duration, BMI (kg/m^2) , AMH ,AFC (D_2), ovulation disorders and numbers of total IVF cycles received.
We observed that average age in all 3 group were nearly similar (group A-34.8/ group B 38.0/ group C 37.9). We also absorbed that infertility duration in years among the three group also had been nearly same (Group A=4.8), (Group B= 4.6),(Group C =5.0) the BMI status in all three group were as (Group A= 23.5), (Group B= 21.9), (Group C = 23.2). We excluded women BMI over 28. The antral follicle count done by transvaginal ultrasound on $D_{2\text{-}3}$ at the cycle revealed that AFC status in (Group A=2.4),(Group B=4.1),(Group C=3.5). Along with their age & infertility duration we found out that ovulation disorders in Group A (32.9) (55/167) and in Group B (10.7) (6/56) and in Group C (11.3)(16/141) was noted the number of IVF cycles received in Group A were 2.5.$^+$_1.5 and in Group B were 2.6$^+$_1.4 and in Group C (3.0$^+$_ 1.7)

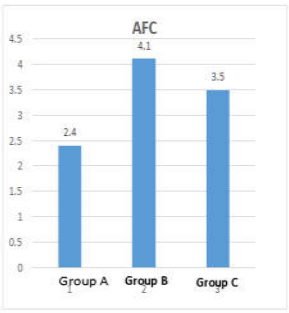
STATISTICAL ANALYSIS (OBSERVATIONS): We evaluated total 364 patients data (Table 1) and observed that the gonadotropin initial dosage starting was in Group A (279$^+$_ 51.9) Group B (260.7$^+$_ 61) Group C(266$^+$_ 72.5) & total days of gonadotropin usage amount to be the same (Group A =2787)(Group B=2701), (Group C=2628) then their laboratory data was read and measurement at E_2, LH,P level were done on the day at trigger with recombinant HCG in all patients.(Table 2). E_2 levels (pmal/lit) in Group A(1819)in Group B(1801) in Group C(1420.6). Their LH valves in (4/L) were in Group A(1.9) in Group B(1.7) in Group C(1.2). We also did their progesterone level on the day at trigger as it has a good prognostic significance. In Group A(1.8) Group B(1.5) Group C(1.6) we also assessed the endometrial thickness in all the patients on day at ET, in Group A (8.4 mm) in Group B(9.6 mm) and Group C(9.1 mm). (Table 2). As all the patients in the study were POR so we had less number of oocytes retrieved. In Group A (3.8$^+$_2.8) in Group B(4.5$^+$_3.0) in Group C(3.9$^+$_2.8). Although the fertilization rate among all three groups was nearby same Group A(77.1% (485/629)Group B(77.6% (194/250) in Group C 71.3% (382/536).(Table 2). By doing ICSI in all cases, high quality embryo M II rate was (60.3% (283/496) in Group A, 63% (121/192) in Group B,62%(230/371) in Group C. The number of embryos available for transfer in Group A (2.2), in Group B(2.7) in Group C(2.2).

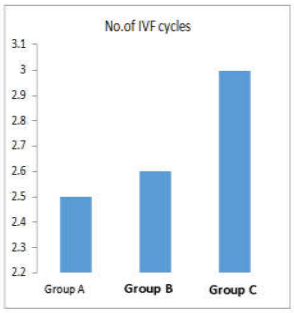






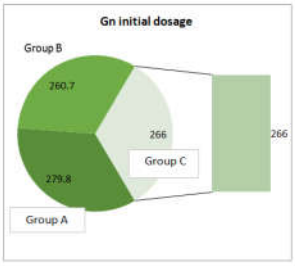


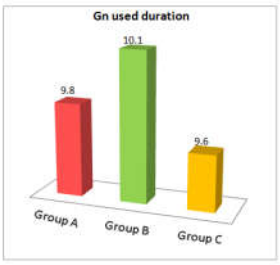


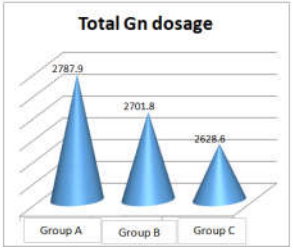


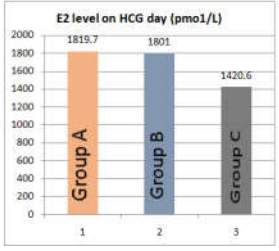
RESULTS

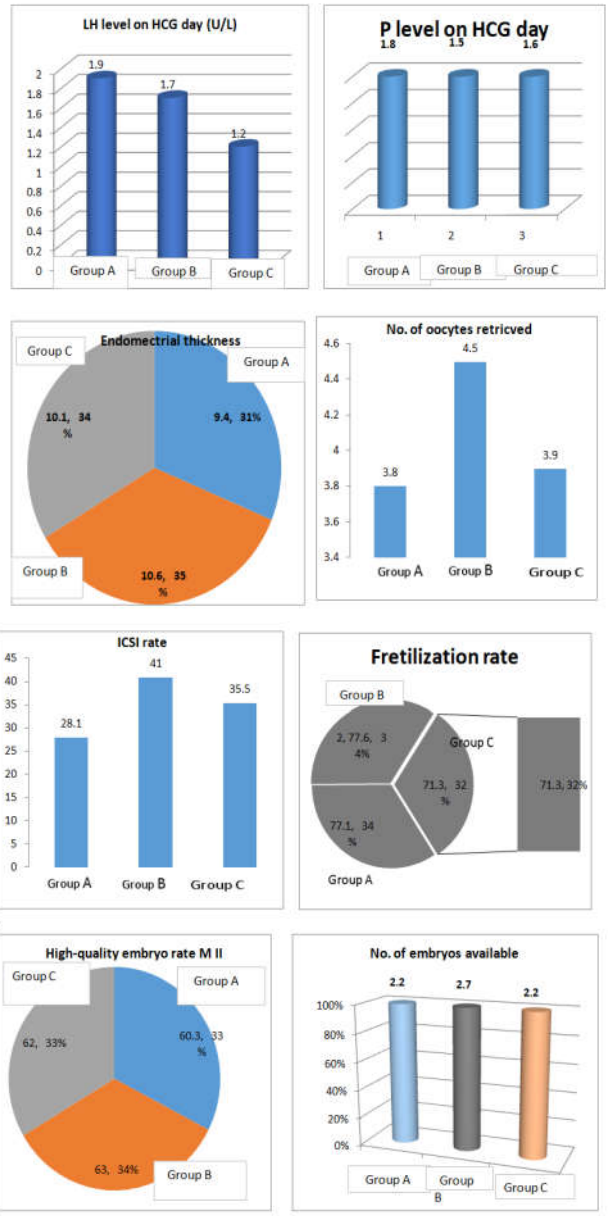
The demographic profile and controlled ovarian stimulation were nearly same for all POR patients were antagonist protocol was used with recombinant HCG in all for trigger and progesterone supplement in luteal phase.











(Table 1) Although the Gn dose duration were nearly similar in all three groups.

Their E_2 /Lh/progesterone value on day at trigger also did not show any p-value significance. The endometrial thickness was also nearly same in all three groups and showed no p-value significance. The number of oocytes retrieved in 3 groups did not show any significance (p-value 0.321). The fertilization rate in all 3 groups also did not show any significance p-value (0.041). The high quality embryo M II after ICSI and number of embryos available for transfer showed no clinical significance, p value (0.783) and (0.266) respectively(Table 2). Although the number of ET cycle and number of embryos transferred were nearly same. The Implantation rate was higher in Group A (26.2% (50/195) and in Group B 26.8% (22/82) as compared in Group C 14.5% (24/166) and showed p value of 0.001 showing clinical significance The clinical pregnancy was also higher in Group A 36.1% (52/167) and in Group B 42% (21/50) as compared to Group C 21.2 %(21/99) and showed p-value of 0.001 showing clinical significance. The abortion rate was lowest in Group A 11.4% (5/44) as compared to 28.6% (6/21) in Group B and 35.5% (5/21) in Group C. Although the biochemical pregnancy rate was lowest in GroupB19.6% (11/56) as compared to Group A 31.1% (52/167) and in Group C 34.0% (48/141)

DISCUSSION

In this study we evaluated the effect at OCP/E_2 pre-treatment prior to GnRh antagonist protocol for cycle scheduling in IVF(1,2,5) we found pre-treatment was associated with longer length of stimulation & increase in total dose of gonadotrophins needed for stimulation (10,11). None of them (OCP/E_2) did not affect the magnitude of ovarian response , in terms of numbers of oocytes retrieved, number and grade of embryos developed & endometrial thickness was not affected but in older women there may have been thinner endometrium following OCP(13,14,15). In our study the implantation Rate & clinical pregnancy were slightly higher in OCP & E_2 group rather in Group 3 with no pre-treatment.(12). Among GroupA & GroupB , the GroupB with E_2 pre-treatments had most clinical pregnancy rates.(6)There were least abortion rate in Group A in OCP group & least biochemical pregnancy in GroupB (E_2Group) (12)

Table 1. General information of patients

item	Group A (N= 167)	Group B (N= 56)	Group C (N=141)	P value
Age (year)	34. 8 + 4.9*	38. 8 + 4. 9	37. 9 + 4. 7	0. 000
Infertility duration	4. 8 + 3. 5	4. 6 + 3. 7	5. 0 + 4. 1	0.807
BMI(Kg/m2)	23. 5 + 3. 6	21. 9 + 3. 1 *	23. 2+ 3. 1	0.014
AMH (ng/ml)	0. 7 + 1. 1	0. 6 + 0. 3	0. 7 + 0. 5	0.888
AFC	2. 4 + 2. 0	4. 1 + 1. 9	3. 5 + 2. 0	0. 000
Ovulation disorders	32. 9 (55/167)*	10. 7 (6/56)	11. 3 (16/141)	0. 000
No.of IVF cycles	2. 5 + 1. 5	2. 6 + 1. 4	3. 0 + 1. 7	0.017

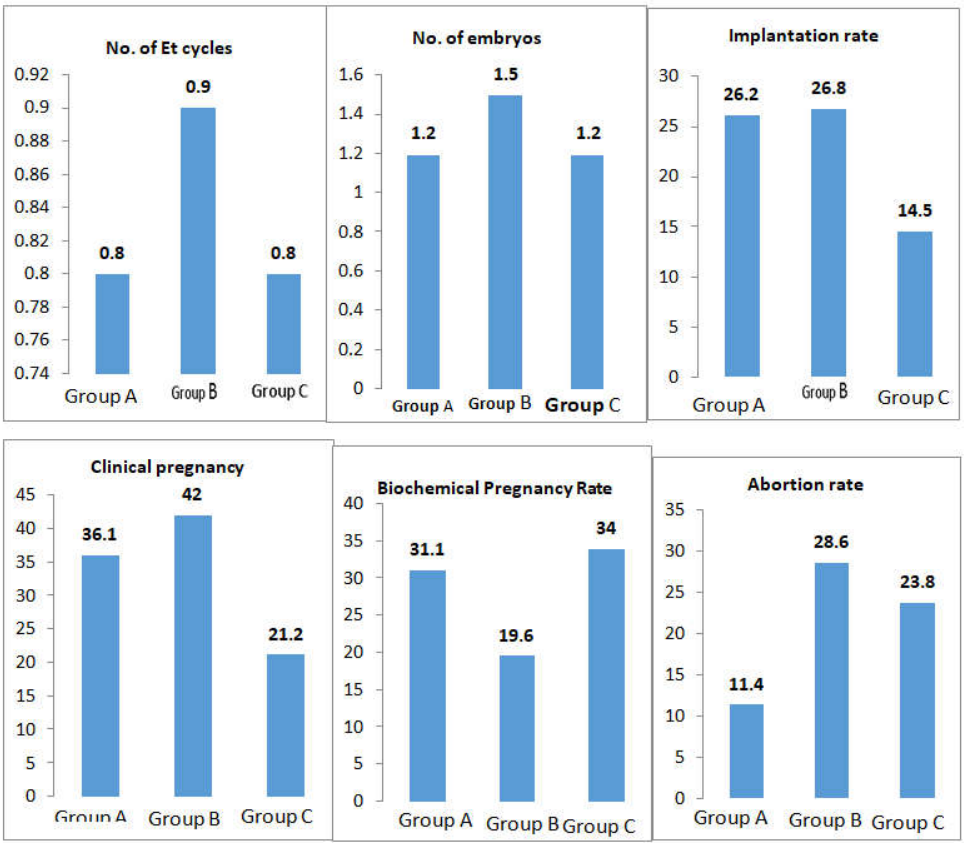
Table 2. COS and laboratory results

Item	Group A	Group B	Group C	P value
Gn initial dosage	279. 8 + 51.9	260. 7 + 61. 0	266. 0 + 72. 5	0. 056
Gn used duration	9. 8 + 2. 6	10. 1 + 2. 4	9. 6 + 2. 7	0. 371
Total Gn dosage	2787. 9 + 931. 5	2701. 8 + 930. 8	2628. 6 + 1049. 7	0. 363
E2 level on HCG day (pmo1/L)	2819. 7 + 1759. 0	2801. 0 + 1845. 4	2420. 6 + 1673. 8	0. 115
LH level on HCG day (U/L)	1. 9 + 3.9	1. 7 + 2. 5	1. 2 + 1. 8	0. 138
P level on HCG day	1. 8 + 1. 0	1. 5 + 0. 8	1. 6 + 1. 4	0. 242
Endometrial thickness	9. 4 + 1.9 *	10. 6 + 1. 5	10. 1 + 2. 0	0. 000
No. of oocytes retricved	3. 8 + 2. 8	4. 5 + 3. 0	3. 9 + 2. 8	0. 321
ICSI rate	28. 1 (47/167)	41. 1 (23/56)	35. 5 (50/141)	0. 148
Fretilization rate	77. 1 (485/629)	77. 6 (194/250)	71. 3(282/536)*	0. 041
High-quality embryo rate (M II)	60. 3 (283/469)	63. 0 (121/192)	62. 0 (230/371)	0. 783
No. of embryos available for transfer	2. 2 + 2. 1	2. 7 + 2. 0	2. 2 + 1. 9	0. 266

Table 3. Embryo transfer and Clinical outcome

Item	Group A	Group B	Group C	p value
No. of Et cycles	0. 8 + 0. 6	0. 9 + 0. 5	0. 8 + 0. 6	0. 225
No. of embryos	1. 2 + 0. 9	1. 5 + 0. 9	1. 2 + 1. 1	0. 154
Implantation rate	26. 2 (50/191)	26. 8 (22/82)	14. 5 (14/166)*	0. 014
Clinical pregnancy	36. 1 (52/167)	42. 0 (21/50)	21. 2 (21/99)*	0. 014
Abortion rate	11. 4 (5/44)	28. 6 (6/21)	23. 8 (5/21)	0. 194
biochemical pregnancy rate	31. 1 (52/167)	19. 6 (11/56)	34. 0 (48/141)	0. 137

ET: embryo transfer. Cycle cancellation includes COS failure , no oocytes retrieved.



CONCLUSION

Pre-treatment prior to GnRh antagonist regimen in expected POR patient with OCP or estradiol valerate in luteal phase can improve the clinical pregnancy outcome of POR patients. Estradiol valerate pre-treatment in luteal phase seems to be more effective than OCP. So if POR patients can be given OCP /E_2 in previous cycle and increase the conception can be beneficial for POR patient OCP & E_2 pre-treatment can be offered as a made for cycle scheduling & increasing clinical pregnancy rates although it may be associated with longer stimulation & higher gonadotropin consumption.

Limitation of study

- The method for menses induction were not assigned randomly, thus selection bias was highly likely because of the study design.
- The mean BMI in this study population were relatively normal, the applicability at this result to obese PCOS women needs to be evaluated in further study.
- There were less number of patients in GroupB (estrogen valerate) group where bias can be found during statistical evaluation.

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