A prospective and retrospective analysis of POSEIDON stratification to predict low prognosis patients during ART cycles in Indian population

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Abstract

Objective: A Prospective and retrospective analysis of POSEIDON stratification to predict low prognosis patients during assisted reproductive technique (ART) cycles in Indian Population. **Design**: Bidirectional Study (Prospective as well as Retrospective). **Setting**: Southend fertility and IVF centre, New Delhi. **Patient Selection**: All Low prognosis patients according to POSEIDON stratification. **Duration of Study**: 06 Months. **Outcome**: Prevalence of Low prognosis patients in Indian Population and Clinical Pregnancy Rate in whom fresh embryo transfer was done. **Results**: In this bidirectional study we enrolled a total 456 patients who underwent ovarian stimulation for ART at Southend Fertility and IVF Centre from Jan 2017 to Dec 2018. Out of these patients 218 (47%) patients were classified as 'low prognosis' according to the POSEIDON criteria. Overall in all four groups Clinical Pregnancy rate was approximately 20.6% in low prognosis patients who underwent fresh ET. **Conclusion**: Providing IVF pregnancy with autologous oocytes to low ovarian responders is the most challenging part of fertility care. The new POSEIDON concept is helping the clinicians in medical management and in counselling patients what to expect, helping in reducing time to pregnancy.

Keywords: ART (Assisted Reproductive Technique), AFC(Antral follicular Count), AMH (Anti Mullerian hormone), ET (Embryo Transfer), GnRH (Gonadotropin releasing hormone), GnRHant protocol (Gonadotropin releasing hormone antagonist protocol), HCG (human chorionic gonatropin), ICSI (Intra cytoplasmic sperm injection), IVF (In vitro fertilisation), LPP (Low prognosis patients), POR (Poor ovarian responders), POSEIDON (Patient Oriented Strategies Encompassing Individualized Oocyte Number)

INTRODUCTION

The reported prevalence of low prognosis patients in women undergoing assisted reproductive technique (ART) stimulation is between 9% and 25%.[1] Success is seemingly low in patients undergoing ART, responding in a poor manner to ovarian hyper-stimulation.[2] For ART success, the rate limiting factor is poor ovarian response, which remains the major challenge of reproductive medicine in modern times. To limit and minimise the requirement for egg donation, early detection of poor ovarian responders (POR) and their active management is of paramount importance.

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Evaluating low prognosis patients is just akin to opening a Pandora's box. It is a nightmare for patient as well for clinician. In the past, nearly 41 efforts have been made to define and classify POR (low prognosis patients).[3] In 2011, Bologna criteria were described, which defined low prognosis patients on basis of ovarian reserve, previous response to stimulation and, most important, age. It did not suggest any recommendation for clinical management and the patient data was of a heterogeneous population.[3]

In absence of any clear definition and to provide homogeneity, in 2015, patient-oriented strategies encompassing individualised oocyte number (POSEIDON) group from seven different countries was introduced. POSEIDON classification is stratification based upon individualised management and prognosis to move patients from low to normal prognosis category.[4] Positive outcome is based on ability to extract the maximum number of oocytes necessary to obtain at least single blastocyst (euploid) for transfer in each patient.[4]

The two factors of POSEIDON's classification are diagnosis and management. The POSEIDON stratification can differentiate among good ovarian reserve women (exogenous stimulation showed unexpected poor response) and poor ovarian reserve women (with expected poor ovarian response). Four subgroups have been recommended depending on ovarian biomarkers, previous low ovarian response and age.[4]

POSEIDON's classification serves as a guide to individualise treatment protocol like tailoring follicular stimulating hormone (FSH) starting dose, personalising gonadotropin dose, gonadotropin releasing hormone (GnRH) analogue regimen and evaluating better strategies (including oocyte/embryo collection) to maximise the outcome in each patient.[5]

This stratification was created to improve treatment outcome and to guide clinicians to deal and counsel poor responder women in an appropriate manner.

The main aim of this study is to evaluate the prevalence of POR using POSEIDON stratification in Indian population during ART treatment.

This new idea of low prognosis/low prognosis patients is helping the clinicians to improve the overall management of women undergoing ART, promoting an individualised

approach for clinical trials and for patient management as it identifies homogenous populations, thereby maximising IVF success rates with better tools.

PERIOD OF THE PROPOSED STUDY

The duration of this study was 6 months (5 months for clinical work and 1 month period for documentation and statistical analysis).

AIMS AND OBJECTIVES

This article evaluates application of POSIEDON criteria for detection of low prognosis patients in Indian population.

Primary outcome
The primary outcome was to calculate prevalence of low prognosis patients in Indian population during ART using POSIEDON stratification.

Secondary outcome
The secondary outcome was clinical pregnancy.

MATERIALS AND METHODS

Women with primary and secondary infertility were recruited from infertility clinic at Southend Fertility and IVF centre, New Delhi. All women with normal investigations specific to infertility having poor response to controlled ovarian stimulation independently of aggressiveness of protocol were enrolled in this study. Based upon their response, they were categorised into four groups according to POSEIDON stratification.

Sample size
A total of 456 patients undergoing ART (270 retrospectively and 186 prospective) were enrolled in this study.

Inclusion criteria
In this bidirectional (combined prospective and retrospective) study, the history and laboratory investigations of 456 women were reviewed to screen for low prognosis patients. In retrospective arm (January 2017 to July 2018), the file records of 270 patients was screened to determine the number of low prognosis patients and in the prospective arm (August 2018 to December 2018), 186 patients were screened for low prognosis patients as per POSEIDON stratification.

Patients were selected depending upon their response to controlled ovarian stimulation and were categorised into four groups based on the POSEIDON classification.[10]

Table 1: POSEIDON classification

POSEIDON classification			Age	AMH	AFC	Subgroup
Good ovarian reserve	Group 1		<35	>1.2	>5	1a) <4 oocytes 1b) 4–9 oocytes
	Group 2		≥35	>1.2	>5	1a) <4 oocytes 1b) 4–9 oocytes
Poor ovarian reserve	Group 3		<35	<1.2	<5	
	Group 4		≥35	<1.2	<5	

Table 2: Classification of prospective and retrospective data according to POSEIDON groups

	Prospective data (N = 80)	Retrospective data (N = 138)
Group 1	33 (41.3%)	60 (43.5%)
Group 2	16 (20%)	43 (31.2%)
Group 3	9 (11.3%)	12 (8.7%)
Group 4	22 (27.5%)	23 (16.7%)

Table 3: Indication of ART in two arms

Causes	Prospective	Retrospective
Low prognosis patients	25	35
Low prognosis patients plus other factors	13	20
Endometrial factors	18	26
Tubal factors	17	26
PCOS	5	21
Male factors	9	24
Unexplained factors	10	22

ART, assisted reproductive technique; PCOS, polycystic ovarian syndrome.

POSEIDON classification
Table 1

Exclusion criteria
This included severe oligozoospermia, azoospermia, frozen embryo transfer cycles and patients with chromosomal errors requiring pre-implantation genetic screening/diagnosis.

Methodology
Different stimulation protocols were used for ovarian stimulation. Oocyte retrieval performed 34 to 36 hours after administration of trigger (human chorionic gonadotropin, hCG). *In vitro* fertilisation or intracytoplasmic sperm injection was done accordingly. The quantities as well as quality of retrieved oocytes (metaphase II, MII) were judged, followed by number and grading of embryos on day 2/3 of fertilisation. Only fresh cycles were included. The best embryos were selected and graded as per standard guidelines. Embryos were transferred on day 2, 3 or 5 under ultrasound guidance. Luteal phase support was given to all patients with dydrogesterone 10 mg twice daily and progesterone gel 8% (90 mg) once a day until onset of menstruation, or 10 weeks after fresh embryo transfer in clinical pregnancy cases. β-hCG levels were checked after 16 days after fresh embryo transfer. Also, ultrasonography (transvaginal) was done 21 days following a positive β-hCG test for confirmation of the presence of clinical pregnancy (a G-sac along with cardiac activity).

Data collection
Data of all the low prognosis patients were collected, which included women's age, duration of infertility and indication of ART. Clinical and laboratory investigations of ART cycles were also noted. The prevalence of low prognosis patients in each group was the primary outcome parameter to ovarian hyper-stimulation.

Clinical pregnancy was considered as the secondary outcome parameter considered.

Statistical analysis
Data analyses were done using the SPSS version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) (for Windows). Nominal variables were analysed using analysis of variance. $P < 0.05$ was considered statistically significant.

RESULTS

In this bidirectional study, data of 456 patients were analysed who underwent ART stimulation with us for over a period of 2 years, January 2017 to July 2018, retrospectively, and from August 2018 to December 2018, prospectively. Out of these 456 patients, 218 (47%) were low prognosis patients according to POSEIDON stratification.
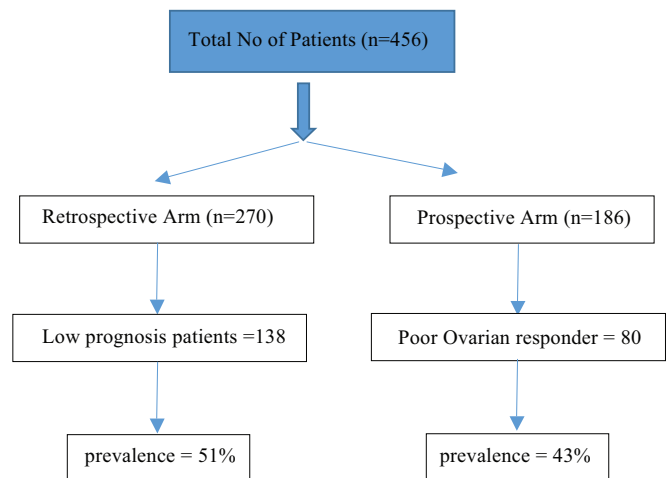
In retrospective arm 138 patients and in prospective arm 80 patients behaved as low prognosis patients.

Table 4: Prospective data (demographic profile and stimulation characteristics; *N* = 80)

Variables	Group 1	Group 2	Group 3	Group 4	*P* value
Age (years)	31.00 ± 2.18	36.75 ± 3.71	30.00 ± 2.95	39.68 ± 2.88	<0.001
Duration of infertility (years)	4.18 ± 1.26	8.25 ± 2.60	4.78 ± 1.39	10.18 ± 4.06	<0.001
Total dose of gonadotropins	3135.99 ± 988.89	3337.50 ± 771.20	1891.67 ± 1544.24	2770.46 ± 1398.35	0.064
Stimulation duration (days)	10.64 ± 2.03	10.25 ± 2.24	8.78 ± 1.79	10.41 ± 1.79	0.107
E2 on trigger day	2549.48 ± 1380.1	1559.74 ± 780.84	957.11 ± 808.07	787.41 ± 560.78	0.001
Oocytes retrieved	6.61 ± 1.56	5.25 ± 2.11	3.22 ± 1.09	3.14 ± 1.49	0.001
MII oocytes	4.73 ± 1.55	3.88 ± 1.59	2.56 ± 1.24	2.33 ± 1.11	0.001
No. of embryos formed	4.30 ± 1.88	3.50 ± 1.71	2.44 ± 1.33	2.00 ± 1.20	0.001
No. of transferred embryos	2.68 ± 0.69	2.25 ± 1.06	2.50 ± 0.84	1.77 ± 0.77	0.015
IVF/ICSI	18/15	6/10	8/1	12/8	–

Analysis represented as mean ± standard deviation. E2, estradiol; ICSI, intra cytoplasmic sperm injection; IVF, *in vitro* fertilisation; MII, metaphase II oocytes.

Table 5: Retrospective data (demographic profile and stimulation characteristics; *N* = 138)

Variables	Group 1	Group 2	Group 3	Group 4	*P* value
Age (years)	30.78 ± 2.58	37.26 ± 2.51	31.25 ± 3.59	39.04 ± 3.19	<0.001
Duration of infertility (years)	4.25 ± 1.36	7.63 ± 2.24	5.33 ± 1.30	9.17 ± 2.55	<0.001
Total dose of gonadotropins	3178.75 ± 797.83	3163.6 ± 1111.31	3391.67 ± 758.31	2765.22 ± 1446.97	0.486
Stimulation duration (days)	10.63 ± 1.56	10.42 ± 1.81	10.75 ± 1.05	10.3 ± 1.11	0.669
E2 on trigger day	2030.38 ± 1354.63	1967.63 ± 1193.26	978.75 ± 686.41	820.35 ± 621.35	<0.001
Oocytes retrieved	6.17 ± 1.74	6.02 ± 1.99	3 ± 1.21	2.83 ± 1.26	<0.001
MII oocytes	4.65 ± 1.84	4.47 ± 2.03	2.17 ± 0.83	2.17 ± 1.11	<0.001
No. of embryos formed	4.4 ± 1.98	4.35 ± 2.09	2.08 ± 0.9	2.14 ± 1.16	<0.001
No. of transferred embryos	2.3 ± 0.59	2.33 ± 0.66	2 ± 0.82	1.84 ± 0.77	0.046
IVF/ICSI	32/28	31/12	8/4	18/5	–

Analysis represented as mean ± standard deviation. E2, estradiol; ICSI, intra cytoplasmic sperm injection; IVF, *in vitro* fertilisation; MII, metaphase II oocytes.

Table 6: Clinical pregnancy rate in different groups in prospective arm

Group	1 (*n* = 33)	2 (*n* = 16)	3 (*n* = 9)	4 (*n* = 22)
Clinical pregnancy rate	(30.7%)	(25.0%)	(11%)	(13%)

According to POSEIDON stratification, we categorise all the low prognosis patients prospectively and retrospectively into four groups as per their AGE, AMH and AFC [Table 2].

Demographic and stimulation features of the 4 groups of both prospective and retrospective arms are listed in Tables 3, 4, 5 and 6.

There was significant difference in age, duration of infertility, E2 on the day of trigger, oocytes retrieved, number of MII oocytes and number of embryos formed between four groups in both prospective as well as retrospective arm.

Total dose of gonadotropins used and total duration of stimulation were comparable between groups in both arms (P > 0.05).

Cycles got cancelled in five (6%) patients in prospective arm and eight (5.7%) patients in retrospective arms either because of fertilisation failure, arrest at 2 pronucleus (2PN) stage or degeneration of embryos.

Sixteen (20%) patients in the prospective arm and 31 (22%) patients in the retrospective arm did not go for fresh embryo transfer either because of poor endometrial thickness, raised progesterone on the day of trigger or not willing for fresh transfer [Figure 1–2].

In prospective arm 59 patients and in retrospective arm 99 patients went for fresh embryo transfer and out of these 21 (35.5%) and 24 (24.4%) patients, respectively, had clinical pregnancy (presence of gestational sac with cardiac activity) [Tables 6 and 7].

Overall, clinical pregnancy rate in low prognosis patients was approximately 20.6% [Table 8].

DISCUSSION

Introduction of POSEIDON emphasizes on the ability to retrieve the number of oocytes necessary to achieve at least one euploid embryo for transfer in each patient. This model not only helps clinicians in medical management but also in counseling patients for what to expect and helping in reducing time to pregnancy.
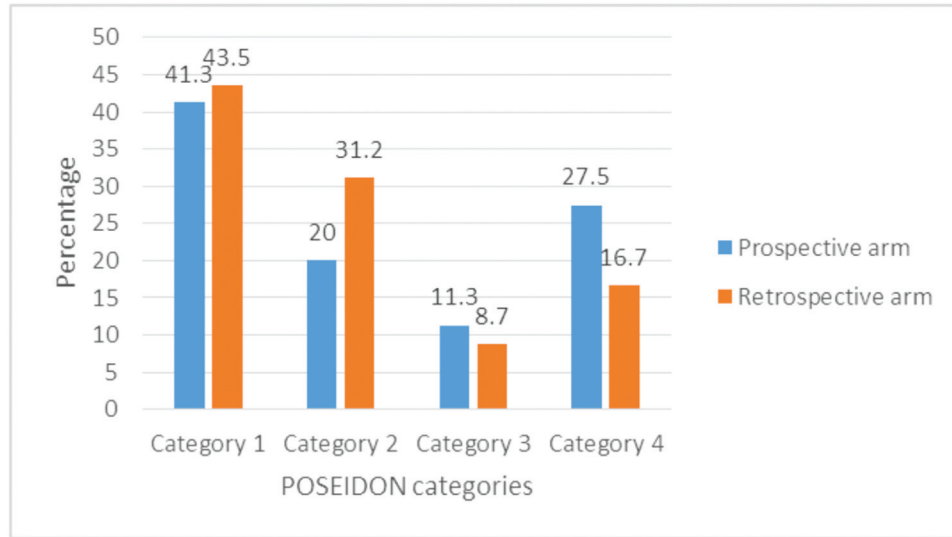
Figure 1: Bar diagram showing distribution of POSEIDON categories in two study arms.
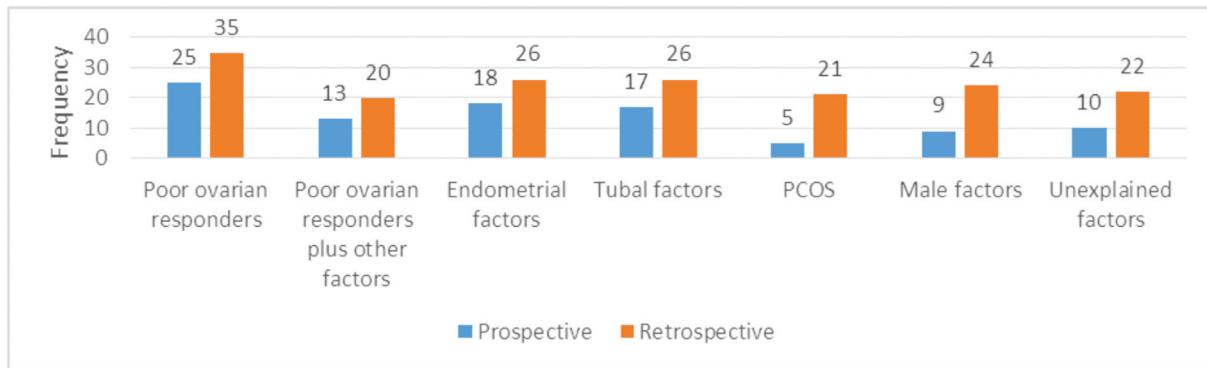

Figure 2: Bar diagram showing ART indication in two arms. ART, assisted reproductive technique.

Table 7: Clinical pregnancy rate in different groups in retrospective arm

Group	1 (n = 60)	2 (n = 43)	3 (n = 12)	4 (n = 23)
Clinical pregnancy rate	(23.3%)	(14%)	(16.6%)	(8.6%)

Table 8: Overall clinical pregnancy rate in different groups in low prognosis patients

Group	1 (n = 93)	2 (n = 59)	3 (n = 21)	4 (n = 45)
Clinical pregnancy rate	(27%)	(17%)	(19%)	(11%)

In this study we enrolled all patients undergoing ART ovarian stimulation and categorized them in prospective and retrospective arms. All patients who responded poorly to ovarian stimulation were then further categorized in 4 groups according to POSEIDON classification.

We observed that overall prevalence of poor ovarian response in prospective arm was 43% and in retrospective arm it was 51%. Hence the prevalence of POR in 2 different cohorts of patients at a given point of time remains almost same. The reported prevalence of low prognosis patients observed by Oudendijk *et al.*[7] varies between 5.6 % and 35.1%.[8] This difference in

prevalence could be explained on basis of ovarian ageing which varies with race and ethnicity as observed by Carlos *et al.*[11]

We used different protocols for controlled ovarian stimulation and the most frequently used was Antagonist (GnRHant) protocol (70%) among all groups. This protocol for pituitary down regulation is advantageous as it causes immediate, rapid gonadotropin suppression by competitively blocking GnRH receptors in the anterior pituitary gland, thereby preventing endogenous premature release of LH and FSH. This significantly shortens treatment duration and lower gonadotropin consumption. Although the meta-anaylsis

done by Jeve and Bhandari did not find any significant difference in the different protocols used.[12]

The clinical pregnancy rate in group 1 and 3 (27% &19% respectively) were better as compare to group 2 and 4 (17% & 11% respectively). This study once again proved age as a rate limiting factor in the success of ART. Age has been described as one of the most significant factors affecting the success of ART in most studies.[6,8]

Results of our study were concordant with a similar observation by Oudendjik JF etal regarding the effect of female age on the prognosis in low prognosis patients showing that older low prognosis patients have lower pregnancy rates (ranging between 1.5 and 12.7%) compared with younger low prognosis patients (ranging between 13.0 and 35%).[8]

Moreover, we observed some patients who had poor response in their previous IVF cycles behave as normal responders in subsequent cycles on changing the type of protocol for controlled ovarian stimulation.

Low ovarian response was observed in some patients with normal ovarian reserve due to suboptimal gonadotropin dose used for ovarian stimulation. This was observed in women with high BMI,[9] or in those who were carriers of genetic polymorphisms which affects the endogenous gonadotropins/receptors. Eventually, the exogenous gonadotropins affect the recruitable follicles.[10]

Finally, it appears that the low prognosis patients cannot be ascribed to a single reason. This population with a decreased ovarian response is therefore diversified and difficult to specify.

CONCLUSIONS

Providing an IVF pregnancy with patient's own oocytes in a POR remains the challenge in fertility treatment. POSEIDON's classification empowers the clinician to first categorize the women with low prognosis (in ART) and subsequently individualize the stimulation plan to obtain optimal number of oocytes needed to obtain one euploid embryo for transfer. This new idea of poor ovarian responders/low prognosis patients is helping the clinicians to improve the overall management of women undergoing ART, promoting an individualised

approach for clinical trials and for patient management as it identifies homogenous populations, thereby maximising IVF success rates with better tools. However, this is only a thesis study. We shall be undertaking larger samples and results may come out to be more defined.

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Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Eftekhar M, Aflatoonian A, Mohammadian F, Eftekhar T. Adjuvant growth hormone therapy in antagonist protocol in low prognosis patients undergoing assisted reproductive technology. Arch Gynecol Obstet 2013;287:1017-21.
2. Kailasam C, Keay S, Wilson P, Ford W, Jenkins J. Defining poor ovarian response during IVF cycles, in women aged <40 years, and its relationship with treatment outcome. Hum Reprod 2004;19: 1544-7.
3. Polyzos NP, Devroey P. A systematic review of randomized trials for the treatment of low prognosis patients: is there any light at the end of the tunnel? Fertil Steril 2011;96:1058-61.e7.
4. Humaidan P, Alviggi C, Fischer R, Esteves SC. The novel POSEIDON stratification of 'Low prognosis patients in Assisted ReproductiveTechnology' and its proposed marker of successful outcome. F1000Research 2016;5:2911.
5. Esteves SC, Roque M, Bedoschi GM, Conforti A, Humaidan P, Alviggi C. Defining low prognosis patients undergoing assisted reproductive technology: POSEIDON criteria—the why. Front Endocrinol 2018;9:461.
6. Bozdag G, Polat M, Yarali I, Yarali H. Live birth rates in various subgroups of low prognosis patients fulfilling the Bologna criteria. Reprod BioMed Online 2017;34:639-44.
7. Tokura Y, Yoshino O, Ogura-Nose S, Motoyama H, Harada M, *et al.* The significance of serum anti-Müllerian hormone (AMH) levels in patients over age 40 in first IVF treatment. J Assist Reprod Genet 2013;30:821-5.
8. Oudendijk JF, Yarde F, Eijkemans MJ, Broekmans FJ, Broer SL. The poor responder in IVF: is the prognosis always poor?A systematic review. Hum Reprod Update 2012;18:1-11.
9. Aflatoonian A, Eftekhar M, Mohammadian F, Yousefnejad F. Outcome of assisted reproductive technology in women aged 40 years and older. Iranian J Reprod Med 2011;9:281-4.
10. Sampo AV, Palena C, Ganzer L, Maccari V, Estofan G, Hernandez M. The adverse effect of overweight in assisted reproduction treatment outcomes. JBRA Assist Reprod 2017;21:212-6.
11. Iglesias C, Banker M, Mahajan N, Herrero L, Meseguer M, Garcia-Velasco JA. Ethnicity as a determinant of ovarian reserve: differences in ovarian aging between Spanish and Indian women. Fertil Steril 2014;102:244-9.
12. Jeve YB, Bhandari HM. Effective treatment protocol for poor ovarian response: a systematic review and meta-analysis. J Hum Reprod Sci 2016;9:70-81.