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Original Article

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Comparison of Cumulative Live Birth Rate (CLBR) According to Patient Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) Stratification Among Low Prognosis Women Undergoing IVF-ICSI Cycles

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Abstract

Background: The purpose of the current study was to evaluate patient-oriented strategies encompassing individualized oocyte number (POSEIDON) criteria, validate stratification of low prognosis women, and prognosticate their reproductive potential in terms of cumulative live birth rate (CLBR) in Indian women.

Methods: Out of 4048 women who underwent IVF/ICSI, 3287 women met the criteria for final evaluation of CLBR. They criteria were divided into (a) group 1a as cases with <4 oocytes retrieved and 1b with 4-9 oocytes retrieved; (b) group 2a as cases with <4 oocytes retrieved and 2b with 4-9 oocytes retrieved; (c) group 3 (<35 years, AMH <1.2 *ng/ml*, AFC <5); and (d) group 4 (≥35 years, AMH <1.2 *ng/ml*, AFC <5). Non-POSEIDON group was sub-divided into normo-responders (10-20 oocytes) and hyper-responder (>20 oocytes).

Results: Overall CLBR was two-fold lower in POSEIDON group as compared to non-POSEIDON group (p<0.001). For every one-year increase in the age, the odds of CLBR decreased by 4% (OR 0.96, CI 0.93-0.99) in POSEIDON group and by 5% (OR 0.95, CI 0.92-0.98) in non-POSEIDON group. For every unit increase in number of oocytes retrieved, the odds of CLBR increased by 1.22 times (OR1.22, CI 1.16-1.28) in POSEIDON group and by 1.08 times (OR 1.08, CI 1.05-1.11) in non-POSEIDON group. Among POSEIDON groups, the highest values in CLBR belonged to group 1b followed by 3, 2b, 4, 1a, and 2a.

Conclusion: POSEIDON stratification of low-prognosis women undergoing IVF may be considered valid to prognosticate and counsel women undergoing IVF. Prospective studies will strengthen its validity among different ethnic populations.

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Introduction

Fertility management of women with decreased ovarian reserve (DOR) or poor ovarian response (POR) is a real challenge for fertility specialists. Although Bologna criteria (1) unified the definition of decreased ovarian reserve (DOR), it contains many shortcomings. The main

drawback was that a young woman who had not undergone any IVF cycle could not be labelled a poor responder even in presence of abnormal ovarian reserve tests (2).

Patient oriented strategies encompassing individualized oocyte number (POSEIDON) criteria were proposed to effectively stratify the reproductive potential of low prognosis women from the perspective of prognosis and reproductive outcomes (3). This criterion classifies the low prognosis women into four different groups depending upon age, ovarian reserve markers (anti-müllerian hormone (AMH) levels and antral follicle count (AFC)), and number of oocytes retrieved in previous cycles if present. These patients might have had normal ovarian reserve parameters (AMH ≥1.2 *ng/ml*; AFC ≥5) but unexpected poor responses (<4 oocytes) or unexpected suboptimal responses (4-9 oocytes) in previous IVF cycles or they might have had abnormal ovarian reserve parameters (AMH <1.2 *ng/ml*; AFC <5) (3).

The most critical end-point for success of an IVF cycle is cumulative live birth rate (CLBR) or cumulative delivery rate (CDR) because fresh embryo transfer may be cancelled due to various reasons and patient may conceive by taking advantage of frozen embryo transfer (FET) cycles. The total number of embryo transfers also increases with the increase in number of retrieved oocytes as there would be optimal number of embryos for transfer (4). Esteves et al. found that the CDR was lower in the POSEIDON patients than in the non-POSEIDON patients (33.7% *vs*. 50.6%; p<0.001) and differed across POSEIDON groups (younger unexpected poor responders as group 1a, n=212, 27.8%; younger unexpected suboptimal responders as group 1b, n=1785, 47.8%; older unexpected poor responders as group 2a, n=293, 14.0%; older unexpected suboptimal responders as group 2b, n=1275, 30.5%; younger expected poor responders as group 3, n=245, 29.4%; and older expected poor responders as group 4, n=623, 12.5%) (4).

Several studies have been published about IVF outcomes in women classified according to POSEIDON criteria and they showed that POSEIDON stratification of low prognosis women creates more homogenous groups and helps to counsel these couples about possible outcomes (5).

But overall, data is sparse and it is necessary to validate POSEIDON stratification among different ethnic groups (6). Indian women have been reported to age 5-6 years faster in comparison to western age matched controls (7). No study has been published on validity of POSEIDON group stratification among Indian women. The present study was planned to evaluate cumulative live birth rate (CLBR) among Indian women undergoing IVF/ICSI classified according to POSEIDON stratification.

Methods

This study was a retrospective cohort conducted in the Assisted Reproduction Technology (ART) clinic of a tertiary care referral center, All India Institute of Medical Sciences (AIIMS), New Delhi, India. Ethical clearance was obtained from the Institute Ethics Committee (IECPG-665/23.12.2020, RT-42/27.01.2021). Women who had undergone IVF between January 2011- December 2020 were screened for the study and their CLBR was recorded.

Study population: The study included all the women who had undergone IVF/ICSI cycle at Assisted Reproduction Technology (ART) center of a tertiary care referral hospital between January 2011 and December 2020. Based on the inclusion criteria, all women aged 21-40 years were recruited who had (a) undergone standard stimulation protocols (antagonist, agonist or microdose flare); (b) undergone oocyte retrieval irrespective of number of oocytes retrieved; and (c) given live birth after fresh ET or FET or had not given live birth after transfer of all embryos available. Women recruited in POSEIDON group were divided into (a) POSEIDON group 1 as women younger than 35 with sufficient pre stimulation ovarian reserve parameters (AFC ≥5, AMH ≥1.2 *ng/ml*) besides unexpected poor or suboptimal ovarian response and the group was further divided into subgroup 1a as women with <4 retrieved oocytes and subgroup 1b as women with 4-9 oocytes retrieved after standard ovarian stimulation; (b) POSEIDON group 2 as women older than 35 years with sufficient pre stimulation ovarian reserve parameters (AFC ≥5, AMH ≥1.2 *ng/ml*) besides an unexpected poor or suboptimal ovarian response and this group was further divided into subgroup 2a as women with <4 retrieved oocytes and subgroup 2b as women with 4-9 oocytes retrieved after standard ovarian stimulation; (c) POSEIDON group 3 as women younger than 35 years with poor ovarian reserve pre stimulation parameters (AFC <5, AMH <1.2 *ng/ml*); and (d) POSEIDON group 4 as women older than 35 years with poor ovarian reserve pre stimulation

parameters (AFC <5, AMH <1.2 *ng/ml*). Non-POSEIDON cases were divided into two subgroups based on oocytes retrieved (10-20 oocytes as normo-responders and >20 oocytes as hyper-responders).

Exclusion criteria were (a) oncofertility preservation cycles, (b) donor-recipient cycles, (c) incomplete data, (d) minimal stimulation cycles, and (e) patients with hypogonadotrophic hypogonadism.

The data used for the study was baseline information about patients' age, BMI, hormonal profile of female partners (FSH, LH, prolactin, AMH), antral follicle count (AFC), and semen analysis of husbands. Those with uncontrolled serum prolactin levels and thyroid disorders were recruited for IVF only after correcting endocrine disorders. Uterine cavity assessment was done using 4D USG of uterine cavity or hysteroscopy. All the investigations were done within 3 months of starting IVF cycle. Ovarian response and type of protocol, starting date and total dose of gonadotrophins, duration of stimulation, oocyte yield, fertilization rate, and clinical pregnancy rate were evaluated from the database. IVF and pregnancy outcomes were collected from the unit database or by phone consultations.

Treatment protocol: All the patients had undergone standard ovarian stimulation treatment including long protocol of administration of gonadotropin-releasing hormone agonist, short GnRH agonist protocol (microdose flare-up), and GnRH antagonist protocol.

Ovarian stimulation and embryo transfer procedure: Recombinant FSH (Gonal-F, Merck Serono, Italy) and/or human menopausal gonadotropin (Humog, Menotropins, Bharat Serums and Vaccines Limited, India) was initiated on menstrual cycle day 2 or 3. The starting dose was selected based on age, body mass index, anti-müllerian hormone (AMH), basal FSH, and antral follicle count (AFC). Gonadotropin dose was further adjusted according to size and number of growing follicles observed by ultrasound, and serum estradiol level during monitoring of stimulation. Recombinant hCG (Ovitrelle 250 *µg*, Ovitrel; Merck Serono, Italy)/ leuprolide acetate 2 *mg* (leuprolide acetate, Lupride, Sun Pharma, India) was administered to trigger the final oocyte maturation, when at least three dominant follicles measuring ≥18 *mm* in diameter were observed on ultrasound. In dual trigger cycles, hCG 150-250 *µg* and leuprolide acetate 1-2 *mg*, a GnRH agonist, were used in combination.

Transvaginal ultrasound-guided oocyte retrieval was done 34-36 *hr* after the trigger. Oocytes were inseminated or injected (ICSI) with the respective husband's spermatozoa or donor sperm in cases of non-obstructive azoospermia and obstructive azoospermia, where the couple refused or experienced failure in surgical sperm retrieval and opted for donor sperm. Fertilization check was done 16-18 *hr* after insemination. Further cleavage was assessed and embryos were graded as per Istanbul consensus (8) and blastocyst grading was done according to Gardner and Schoolcraft blastocyst scoring system (9).

Up to a maximum of 2 good-quality embryos were transferred on day 2, 3, or 5 under ultrasound guidance using a soft embryo transfer catheter (Cook Medical Australia, Australia). Surplus embryos were frozen by vitrification for future use. Elective freezing of all embryos was carried out in patients at risk of ovarian hyperstimulation syndrome, in those with a premature increase in progesterone level on the trigger day (*i.e.*, >1.5 *ng/ml*), thin endometrium, accumulation of intrauterine fluid, endometrial polyps, and medical causes like fever, deranged TSH, blood sugar, *etc.* Luteal support was given with intramuscular injections of progesterone 100 *mg* daily (Susten, Sun Pharma, India) or vaginal micronized progesterone 400 *mg* twice a day for two weeks. Serum β hCG was checked 16 days after embryo transfer and clinical pregnancy was confirmed for those with a positive β hCG by transvaginal sonography 4 weeks after embryo transfer. The patients were followed up in antenatal clinics subsequently till delivery. No other analyses concerning obstetric and neonatal outcomes were carried out.

Outcome measures: The main outcome measure was cumulative live birth rate (CLBR) per stimulation cycle. The numerator was defined as number of live births resulting from fresh/frozen embryo transfer cycles. Patients having more than one live birth were considered as one case. Denominator was defined as all the patients who had undergone oocyte aspiration and have either achieved at least one live birth or whose embryos had been exhausted. Therefore, patients who still had frozen embryos left were excluded from the primary outcome analysis (CLBR). Secondary outcome measures were oocyte yield, MII oocytes, fertilization, cleavage and implantation rate, and cumulative clinical pregnancy rate.

Clinical pregnancy was defined as a pregnancy diagnosed by ultrasonographic visualization of

one or more gestational sacs or definitive clinical signs of pregnancy at 6-7 weeks (10). Total pregnancy rate (TPR) was defined as the total number of pregnancies recorded including biochemical pregnancy and the denominator (initiated, aspirated, or embryo transfer cycles) was specified (10). Cumulative live birth (CLBR) was defined as the number of deliveries with at least one live birth resulting from one initiated or aspirated ART cycle, including all cycles in which fresh and/or frozen embryos are transferred, until one delivery with a live birth occurs or until all embryos are used, whichever occurs first. The delivery of singleton, twin, or other multiple pregnancies is registered as one delivery (10).

Statistical analysis: Data analysis was carried out using statistical software STATA *vs*. 15.1 (StataCorp LLC, US). Quantitative data were presented as mean±standard deviation or median (interquartile range) if applicable. Categorical data were summarized using the frequency and percentages. The quantitative data were analyzed using one-way ANOVA (or Kruskal–Wallis) or independent samples t-test (or Wilcoxon rank sum test) depending on the number of groups and normality assumptions if applicable. To investigate associations between categorical variables, Pearson's chi-square test or a Fisher's exact test was used. To assess the association between pairs of groups (out of groups 1-8), multiple chi-square tests were used and the alpha (level of significance) was adjusted using Bonferroni correction which suggests division of prefixed alpha (0.05 or 5%) by the number of comparisons (totally 12 comparisons). A stepwise logistic regression with p-to-remove of 0.20 was used for investigating the factors associated with cumulative live birth rate (CLBR). Women parameters like age, BMI, AFC, AMH, gonadotropin used, infertility factor, trigger, and number of oocytes retrieved were the independent variables. CLBR was considered as the response variable. The findings were reported as unadjusted and adjusted odds ratios (OR) with a 95% CI.

Results

A total of 4048 ART cycles were done during the period of January 2011 and December 2020. Figure 1 presents the consort diagram of the study participants. Out of 3375 IVF cycles included in the study, 88 women were excluded from the final outcome evaluation due to lost to follow up (n=33) and those who had no pregnancy but frozen embryos left (n=55). Therefore, for final outcome evaluation, 3287 women were analyzed. The CLBR was calculated as per aspiration cycle in 3287 women. There was a total of 2929 fresh transfers and 1072 frozen transfers.

The CLBR was also calculated using the non-parametric Kaplan–Meier method and uncensored values (known final outcome). The "time" response in the model was the order of ETs; each patient was the unit of observation, whereas live birth delivery was the event. Time-to-event plots and their corresponding tables were generated using three approaches as follows:

1. A time-to-event analysis of all POSEIDON patients and non- POSEIDON patients (stratified according to oocytes retrieved as normo-responders (10-20 oocytes retrieved) and hyper-responders (>20 oocytes retrieved) (Figure 2).
2. A time-to-event analysis of all POSEIDON patients, combined into a single group and non-POSEIDON groups combined into single group (Figure 3).
3. A time-to-event analysis of all POSEIDON patients, grouped according to age <35 years (younger group) and ≥35 years (older group) and non-POSEIDON patients, also grouped into <35 years (younger group) and ≥35 years (older group) (Figure 4).

For Kaplan-Meier graphs, further 209 women were excluded where ET did not happen due to empty follicle syndrome, fertilization failure, and cleavage failure; therefore, 3028 cases were finally included and CLBR per ET was calculated.

Table 1 shows the baseline characteristics of the patient population. Ages of POSEIDON group 1 and 3 were comparable to non-POSEIDON groups while group 2 and 4 had significantly higher age than non-POSEIDON groups. Female factor was the most common cause of infertility among all the groups. Table 2 shows the baseline investigations of the study participants. Agonist was the most common stimulation protocol used in all POSEIDON and non–POSEIDON groups, except POSEIDON group 1a and group 4 where antagonist protocol was the most common protocol.

As shown in table 2, oocytes retrieved and MII oocytes were significantly higher in non-POSEIDON groups as compared to POSEIDON groups ($p<0.001$). Follicle-to-oocyte index (FOI) was significantly higher in non-POSEIDON groups in comparison to all POSEIDON groups; however, the difference was not statistically significant in POSEIDON group 3 when compared to

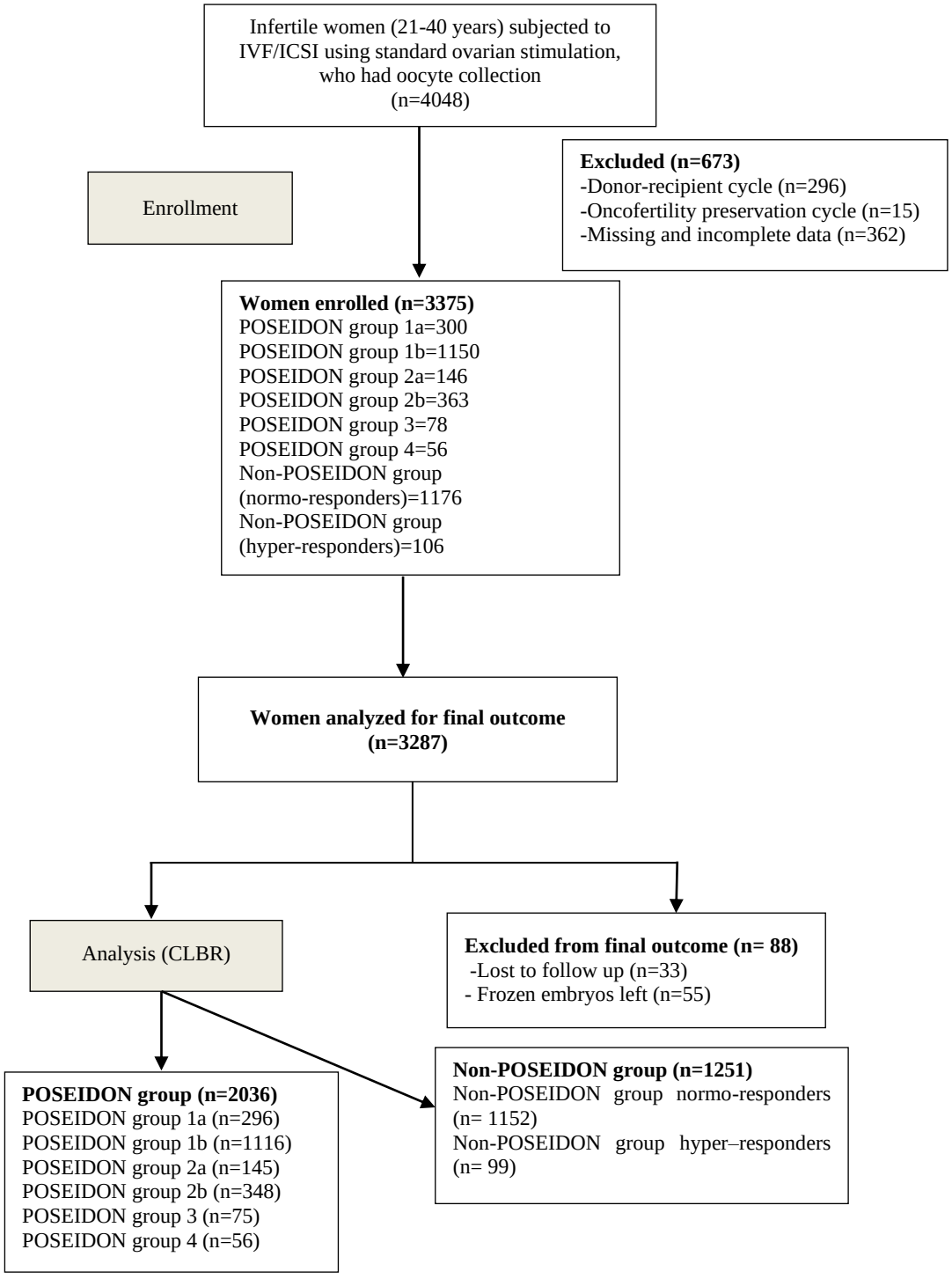

Figure 1. Consort diagram of the study

hyper-responders. The frequency of empty follicle syndrome (EFS) was the highest in group 1a among POSEIDON groups.

The main outcome, cumulative live birth rate (CLBR), was two-fold lower in POSEIDON group (combined) as compared to non-POSEIDON group (combined) (353/2036, 17.33%; 451/1251, 36.05%, p<0.001) (Table 3).

Logistic regression analysis: A regression analysis was done to see the relationship between women parameters like age, BMI, AFC, AMH, gonadotropin used, infertility factor, trigger, number of

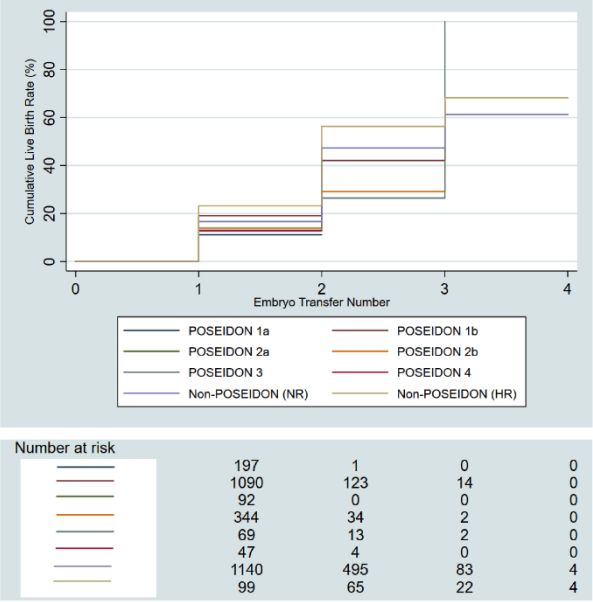

Figure 2. The Kaplan-Meier CLBR plot among POSEIDON and non-POSEIDON groups (divided according to oocytes retrieved).
NR= Normo-responder and HR= Hyper-responder

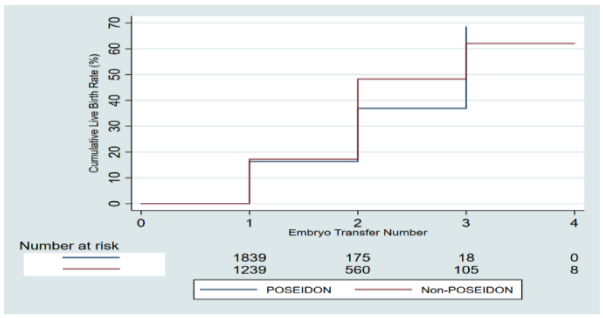

Figure 3. The Kaplan-Meier CLBR plot among combined POSEIDON and non-POSEIDON groups

oocytes retrieved and cumulative live birth rate in POSEIDON and non-POSEIDON group. In non-POSEIDON group, gonadotropin dose, AFC, infertility factor, AMH, protocol, BMI, and trigger were dropped from the model suggesting no relation, whereas age and oocytes retrieved showed significant relationship with cumulative live birth rate. In POSEIDON group, gonadotropin dose, AFC, infertility factor, AMH, BMI, and trigger were dropped from the model, suggesting no association, whereas age, oocytes retrieved, and protocol had significant relationship with cumulative live birth rate.

For every one-year increase in the age, the odds of CLBR decreased by approximately 4% (OR 0.96, CI 0.93-0.99) in POSEIDON group and by

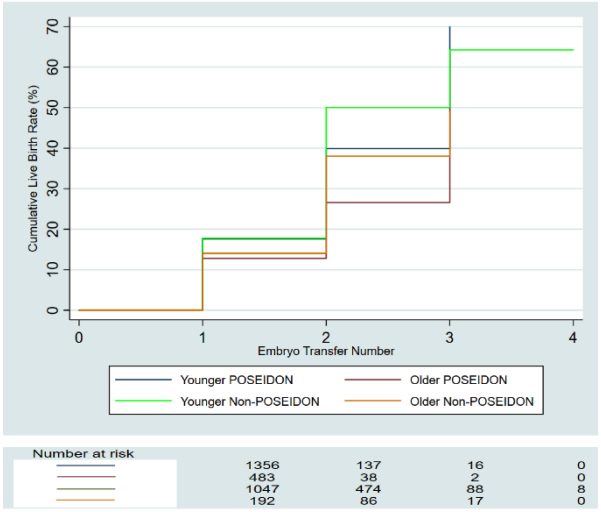

Figure 4. The Kaplan-Meier CLBR plot among POSEIDON and non-POSEIDON groups [Both grouped according to age: younger (<35 years) and older (≥ 35 years)]

5% (OR 0.95, CI 0.92-0.98) in non-POSEIDON group, probably because of oocyte quality, whereas for every unit increase in oocytes retrieved, the odds of CLBR increased by 1.22 times (OR1.22, CI 1.16-1.28) in POSEIDON group and by 1.08 times (OR1.08, CI 1.05-1.11) in non-POSEIDON group. Increased number of oocytes leads to creation of supernumerary embryos which can be cryopreserved for later use and subsequent multiple embryo transfer, thereby the chance of live birth would be enhanced. In POSEIDON group, agonist protocol increases the odds of CLBR 1.30 times (Table 4).

Considering only one ET was done, the probability of having live birth was maximum in POSEIDON group 1b (19%) followed by POSEIDON group 2b (14%), followed by POSEIDON group 3 (13%), followed by group 4 (13%), followed by group 1a (11%), and the chance was the lowest in POSEIDON group 2a (9%). Among non-POSEIDON groups, hyper-responder group had higher cumulative live birth rate as compared to normo-re-sponders (23%, 17%) (Figure 2 and supplementary table 3).

When all POSEIDON groups were combined together and compared with combined non-POSEIDON group for CLBR, the probability of CLBR was higher in non-POSEIDON group than POSEIDON group (17%, 16%) when one ET was done (Figure 3 and supplementary table 4). But overall, CLBR was almost more than double the rate in POSEIDON group. This may be explained by a greater number of oocytes and embryos

Table 1. Comparison of baseline characteristics of POSEIDON with non-POSEIDON group

Baseline characteristics	POSEIDON groups (n=2093)						Non-POSEIDON (normo-responder) group	Non-POSEIDON (hyper- responder) group	Comparison of POSEIDON groups with non-POSEIDON normo-responder group (p-value)						Comparison of POSEIDON groups with non-POSEIDON hyper-responder group (p-value)					
	Group 1 (n=1450)		Group 2 (n=509)		Group 3 (n=78)	Group 4 (n=56)														
	1a (n=300)	1b (n=1150)	2a (n=146)	2b (n=363)	3 (n=78)	4 (n=56)	(n=1176)	(n=106)	1a	1b	2a	2b	3	4	1a	1b	2a	2b	3	4
Age *(years)	30.26±2.81	29.98±2.77	36.62±1.49	36.61±1.59	30.57±2.78	37.12±1.71	30.71±3.64	29.20±3.20	0.615	<0.001	<0.001	<0.001	1.000	<0.001	0.199	0.469	<0.001	<0.001	0.220	<0.00
BMI * (kg/m^2)	24.51±3.21	24.54±3.39	25.28±3.69	25.44±3.54	24.86±3.38	27.13±3.54	24.87±3.40	24.34±3.75	0.919	0.631	0.966	0.358	1.000	0.002	1.000	1.000	0.704	0.293	0.994	0.001
Infertility n (%) $																				
Primary	265 (88.33)	1048 (91.13)	127 (86.99)	317 (87.33)	74 (94.87)	52 (92.86)	967 (82.23)	91 (85.85)	0.011	<0.001	0.164	0.024	0.003	0.042	0.495	0.081	0.853	0.743	0.053	0.212
Secondary	35 (11.67)	102 (8.87)	19 (13.01)	46 (12.67)	4 (5.13)	4 (7.14)	209 (17.77)	15 (14.15)												
Cause of infertility n (%) $																				
Male	53 (17.67)	233 (20.26)	19 (13.01)	60 (16.53)	16 (20.51)	9 (16.07)	207 (17.60)	10 (9.43)	0.042	0.424	<0.001	<0.001	0.758	0.816	0.001	0.003	<0.001	<0.001	0.028	0.360
Female	163 (54.33)	682 (59.30)	74 (50.68)	189 (52.07)	46 (58.97)	38 (67.86)	726 (61.73)	81 (76.42)												
Unexplained	67 (22.33)	180 (15.65)	45 (30.82)	105 (28.93)	14 (17.95)	8 (14.29)	188 (15.99)	10 (9.43)												
Combined	17 (5.67)	55 (4.78)	8 (5.48)	9 (2.48)	2 (2.56)	1 (1.79)	55 (4.68)	5 (4.72)												
FSH * (*mIU/ml*)	6.59 ±2.15	6.33±2.04	6.59±2.02	6.35±1.81	6.41±2.24	7.46±2.41	5.61±1.57	5.47±1.63	<0.001	<0.001	<0.001	<0.001	0.065	<0.001	<0.001	0.005	0.002	0.012	0.128	<0.00
LH # (*mIU/ml*)	4.26 (3.00,5.72)	4.11 (2.92,5.77)	4.10 (2.91,5.78)	4.00 (3,5.52)	3.73 (2.81,4.71)	4.14 (2.86,5.38)	4.49 (3.10,6.09)	5.10 (3.56,7.01)	0.0799	0.0051	0.102	0.016	0.001	0.154	<0.001	<0.001	<0.001	<0.001	<0.001	<0.00
AMH (*ng/ml*)	3.11 (2.30,4.66)	3.42 (2.46,4.92)	2.71 (2,3.72)	2.83 (2.12,4.32)	1.01 (0.81,1.11)	0.99 (0.70,1.09)	4.30 (3.0,6.56)	4.49 (3.19,8.61)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.00
AFC #	11 (8,15)	12 (10,16)	9(7,12)	11(8,14)	9(7,13)	7(6,9)	15(12,20)	34(30,40)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.00

Mean±SD, # Median (p25, p75), $ Bonferroni correction p<0.004 is significant, rest p<0.05 is significant

Table 2. Comparison of ovarian stimulation characteristics and outcome of POSEIDON with non-POSEIDON group

Ovarian stimulation characteristics	POSEIDON groups (n=2093)						Non-POSEIDON (normo- re-sponder) group	Non-POSEIDON (hyper-responder) group	Comparison of POSEIDON groups with non-POSEIDON normo-responder group (P value)						Comparison of POSEIDON groups with non-POSEIDON hyper-responder group (P value)					
	Group 1 (n=1450)		Group 2 (n= 509)		Group 3 (n=78)	Group 4 (n=56)														
	1a (n=300)	1b (n=1150)	2a (n=146)	2b (n=363)	3 (n=78)	4 (n=56)	(n=1176)	(n=106)	1a	1b	2a	2b	3	4	1a	1b	2a	2b	3	4
Stimulation protocol n (%) $																				
Antagonist	143 (47.66)	439 (38.17)	55 (37.67)	142 (39.11)	27 (34.61)	27 (48.21)	474 (40.30)	48 (45.28)												
Agonist	123 (41.00)	676 (58.78)	67 (45.89)	188 (51.79)	37 (47.43)	22 (39.28)	689 (58.58)	58 (54.71)	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	0.080	<0.001	0.001	<0.001	.001
Microdose flare	34 (11.33)	35 (3.04)	24 (16.43)	33 (9.09)	14 (17.94)	7 (12.50)	13 (1.10)	0.00(0.00)												
Total rFSH * (IU)	2673.77 ±1190.23	2823.10 ±1059.36	3096.53 ±1387.79	3135.57 ±1279.33	2970.30 ±1178.53	3365.89 ±1742.51	2655.89 ±977.67	2429.36 ±950.89	1.000	0.069	0.009	<0.001	0.571	0.008	0.798	0.086	0.003	<0.001	0.156	0.001
Total HMG # (IU)	675 (375,2625)	600 (300,1725)	2100 (450,3675)	750 (375,2625)	1087.5 (525,2700)	1612.50 (675,3600)	375 (300,900)	337.5 (225,375)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
E2 # (pg/ml)	1665 (900,2524)	2792 (1958,4280)	1219 (851,2274)	2738 (1772,4361)	2433 (1532,3560)	1221 (766,2550)	4448 (3138,4941)	5085 (4256,7590)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
P4 # (*ng/ml*)	1.14 (0.68,1.9)	1.11 (0.76,1.61	1.02 (0.81,1.81)	1.12 (0.78,1,71)	1.04 (0.7,1.45)	0.91 (0.48,1.32)	1.30 (0.92,1.98)	1.27 (1.06,1.73)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.022	0.001	0.011	0.012	0.002	<0.001
Total stimulation days #	11 (9,12)	11 (10,12)	11 (9,12)	11 (10,12)	10 (10,11)	10 (9,12)	10 (10,11)	10 (9,11)	0.130	0.014	0.141	0.003	0.366	0.078	0.019	0.006	0.990	0.968	0.211	0.418
ET on day of trigger (*mm*)*	8.69±1.72	9.06±1.62	9.12±1.87	9.10±1.75	8.94±1.57	8.60±1.90	9.14±1.65	9.36±1.90	0.013	0.984	1.000	1.000	0.994	0.604	0.087	0.882	0.023	0.001	0.911	0.399
FOI *	0.20±0.16	0.56±0.25	0.26±0.18	0.58±0.23	0.69±0.37	0.52±0.28	0.91±0.42	0.75±0.12	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.981	0.011
Oocyte retrieved #	2 (1,3)	7 (5,8)	2 (1,3)	6 (5,8)	6 (4,10	4 (2,5)	12 (11,15)	24 (22,28)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
MII #	2 (0,2)	5 (3,6)	2 (0,2)	4 (3,5)	4 (3,7)	2 (1,4)	9 (7,10)	17 (15,20)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Fertilization rate *	90.29±29.19	98.26±12.02	84.01±36.30	97.58±14.13	94.57±22.48	92.30±26.90	95.14±14.22	92.35±16.38	0.013	0.007	<0.001	0.577	1.000	0.986	0.988	0.113	0.058	0.358	0.998	1.000
Cleavage rate#	0 (0,100)	100 (47,100)	0 (0,0)	100 (0,100)	100 (83.33,100)	87.50 (0,100)	77.77 (62.50,100)	87.50 (72.22,100)	<0.001	<0.001	<0.001	0.009	<0.001	0.288	<0.001	0.259	<0.001	0.202	0.002	0.034
Total Embryos#	2 (0,2)	4 (3,6)	1 (0,2)	4 (3,5)	4 (2,6)	2 (1,4)	8 (6,10)	15 (11,18)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Vitrified embryos n (%) $	11 (3.67)	227 (19.74)	5 (3.42)	65 (17.91)	15 (19.23)	9 (16.07)	649 (55.19)	88 (83.02)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Day of embryo transfer#	2 (2,3)	3 (3,3)	2 (2,3)	3 (2,3)	3 (2,3)	3 (2,3)	5 (3,5)	5 (5,5)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
EFS n (%)	60 (20.00)	6 (0.52)	22 (15.06)	0 (0.00)	2 (2.56)	4 (7.14)	0 (0.00)	0 (0.00)												
Fertilization Failure n (%)	22 (7.33)	14 (1.21)	19 (13.01)	4 (1.10)	4 (5.12)	4 (7.14)	12 (1.02)	0 (0.00)												
Cleavage failure n (%)	17 (5.66)	6 (0.52)	12 (8.21	0 (0.00)	0 (0.00)	1 (1.78)	0 (0.00)	0 (0.00)												

*Mean±SD, # Median (p25, p75), $ Bonferroni correction P<0.004 is significant, rest P<0.05 is significant

Table 3. Comparison of pregnancy outcomes of POSEIDON groups with non-POSEIDON group

POSEIDON groups (n=2093)							Non-POSEIDON (normo-responder) group	Non-POSEIDON (hyper-responder) group	Comparison of POSEIDON groups with non-POSEIDON normo-responder group						Comparison of POSEIDON groups with non-POSEIDON hyper-responder group					
	Group 1 (n=1450)		Group 2 (n= 509)		Group 3 (n=78)	Group 4 (n=56)														
	1a (n=300)	1b (n=1150)	2a (n=146)	2b (n=363)	3 (n=78)	4 (n=56)	(n=1176)	(n=106)	P value						P value					
Women were excluded due to lost to follow up and no pregnancy but frozen embryos left	n=4	n=34	n=1	n=15	n=3	n=0	n=24	n=7	1a	1b	2a	2b	3	4	1a	1b	2a	2b	3	4
Final women for analysis	n=296	n=1116	n=145	n=348	n=75	n=56	n=1152	n=99												
TPR/aspiration cycle	29 (9.79)	335 (30.01)	10 (6.89)	72 (20.68)	16 (21.33)	10 (17.85)	487 (42.27)	63 (63.63)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CPR/ aspiration cycle	28 (9.45)	312 (27.95)	10 (6.89)	66 (18.96)	16 (21.33)	9 (16.07)	466 (40.45)	62 (62.62)	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CLBR/aspiration cycle	22 (7.43)	249 (22.31)	8 (5.51)	55 (15.80)	13 (17.33)	6 (10.71)	394 (34.20)	57 (57.57)	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CLBR/ET	22/198 (11.1)	249/1227 (20.3)	8/92 (8.7)	55/380 (14.5)	13/84 (15.5)	6/51 (11.8)	394/1722(22.9)	57/190 (30.0)												

TPR = Total pregnancy rate, CPR= Clinical pregnancy rate, CLBR = Cumulative live birth rate

Table 4. Univariate analysis of comparison of different POSEIDON groups with non-POSEIDON groups

	POSEIDON group		Non-POSEIDON group	
CLBR	**Adjusted odds ratio (95% confidence interval)**	**Unadjusted odds ratio (95% confidence interval)**	**Adjusted odds ratio (95% confidence interval)**	**Unadjusted odds ratio (95% confidence interval)**
Age	0.96 (0.93-0.99)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.94 (0.91-0.97)
Oocytes retrieved	1.22 (1.16-1.28)	1.24 (1.18-1.30)	1.08 (1.05-1.11)	1.08 (1.06-1.12)
Stimulation protocol				
Antagonist	Reference	Reference	-	-
Agonist	1.30 (1.01-1.67)	1.46 (1.14-1.86)	-	-
Microdose flare up	1.06 (0.60-1.84)	0.77 (0.14-0.20)	-	-

Table 5. Multivariable logistic regression analysis showing factors affecting CLBR in POSEIDON and non-POSEIDON groups

CLBR	Unadjusted odds ratio (95% CI)	p-value
Non-POSEIDON group (normo-responders and hyper-responders)	Reference	
POSEIDON1a	0.14 (0.09-0.22)	<0.001
POSEIDON1b	0.51 (0.42-0.61)	<0.001
POSEIDON 2a	0.10 (0.05-0.21)	<0.001
POSEIDON 2b	0.33 (0.24-0.45)	<0.001
POSEIDON 3	0.37 (0.09-0.50)	0.001
POSEIDON 4	0.21 (0.50-0.63)	0.002

available in non-POSEIDON group, thus a greater number of total ETs and higher overall CLBR. This further explained the number of available oocytes as the independent factor affecting CLBR. When POSEIDON and non-POSEIDON groups were divided according to age, then younger non-POSEIDON cases had similar CLBR (18%) as younger POSEIDON women (18%) after undergoing at least one ET. In older group, non-POSEIDON women (14%) had better CLBR than POSEIDON women (13%) with at least one ET done (Figure 4 and supplementary table 5).

In comparison to non–POSEIDON group, the highest CLBR was detected in younger suboptimal response group 1b followed by younger poor reserve group 3, older suboptimal response group 2b, older low reserve group 4, younger poor response group 1a, and older poor response group 2a, respectively (Table 3). Table 5 presents the univariate analysis showing different POSEIDON groups and CLBR, taking non-POSEIDON group as the reference.

Regarding sub-group analysis based on age of POSEIDON cohort, younger age group (group 1 and 3) had better outcome in terms of total oocytes retrieved, total MII oocytes, fertilization rate, day 3 cleavage rate, number of cryopreserved embryos, and cumulative live birth rate. Total administered human menopausal gonadotropin (hMG) was significantly higher in the older group (group 2 and 4) (Supplementary table 1).

On dividing the POSEIDON cohort according to ovarian reserve (good reserve group; group 1 and 2) versus (poor ovarian reserve; group 3 and 4), the total gonadotropin dose administered was greater in poor reserve group than good reserve group, whereas they were comparable in terms of total oocytes retrieved, total MII oocytes, fertilization rate, number of cryopreserved embryos, total pregnancy rate, clinical pregnancy rate, and cumulative live birth rate (Supplementary table 2).

Discussion

The present research is the first study to evaluate IVF outcomes in terms of cumulative live birth rate among low prognosis Asian-Indian women undergoing IVF-ICSI cycles. According to the findings, CLBR in POSEIDON patients was almost half of that in non-POSEIDON women. The study showed that among both POSEIDON and non-POSEIDON population, female age and oocyte number are the most important predictors of cumulative live birth rate.

Previous studies done on POSEIDON stratification of women undergoing IVF/ICSI cycles have shown similar results concluding female age and oocyte number as the most important parameters affecting CLBR irrespective of the fact whether the woman belongs to POSEIDON or non-POSEIDON group (11-13).

The single most important parameter affecting oocyte yield and CLBR is the female age. Similar to previously reported studies (14,15), the present study showed significantly higher pregnancy rate and CLBR among young POSEIDON (group 1 and 3) as compared to older POSEIDON (group 2 and 4) groups. When comparing group 2 and 3, it was revealed that although group 2 had higher number of oocytes and embryos, significantly higher CLBR was reported in group 3 than group 2 due to younger age with higher oocyte yield (16). In the present study, group 2 was further

divided into poor (2a) and sub-optimal responders (2b). Therefore, slightly higher CLBR was reported in group 2b (14%) as compared to group 3 (13%). Group 2a demonstrated the lowest CLBR rates among all the POSEIDON groups. Advancing age affects the IVF outcomes by decreasing both oocyte quantity and quality, thus affecting implantation, aneuploidy, and miscarriage rates. Thus, POSEIDON stratification may be of help to the clinicians in counselling low prognosis women planning for IVF treatments.

Different researchers have categorized different groups as comparators to POSEIDON groups either according to both AFC and oocyte (16), or only number of oocytes. Esteves et al. have done the similar stratification and analysis although higher CLBR has been reported in all POSEIDON groups (34%) as compared to the present study (17.33%) (4). This may be due to different patient profiles, different protocols used, ethnic variations, and the effect of socio-demographic factors in different study populations. Indian women have been reported to age 5-6 years faster than western age-matched counterparts which may explain the comparatively lower CLBR in POSEIDON group. Also, in Esteves et al.'s study, all patients with >9 oocytes were considered as a single non-POSEIDON group. Yet, in the present study, non-POSEIDON group was divided into further two groups according to number of oocytes retrieved. Although the number of hyper-responders was comparatively less, this group had the highest CLBR in our study. This may be explained by CLBR as a function of number of oocytes, embryos, and supernumerary embryos available for frozen embryo transfer.

POSEIDON stratification may help to prognosticate women undergoing repeated IVF cycles after failed attempts. Interventions may vary depending upon POSEIDON stratification. In a study by Leijdekkers et al., CLBR rates were calculated among POSEIDON stratified women over repeated IVF cycles. Their CLBR rate was about 56% over 18 months which could be due to repeated IVF cycles (17). This will help to give realistic picture of success rate of repeated IVF cycles.

This is the first study from India assessing IVF outcomes in different POSEIDON groups among women undergoing IVF. CLBR as the primary outcome measure was calculated which is considered the most important and relevant parameter to assess ART success. In fact, large amounts of data were gathered during the 10 years. Our results might add to the existing literature on validation of POSEIDON criteria and help these DOR women in prognosticating and individualizing the treatment for better ART outcomes. Limitations include retrospective nature of the study and male factor was not excluded which could have affected the outcome.

Conclusion

POSEIDON stratification of low prognosis women undergoing IVF stands strong and is valid to prognosticate and counsel the women undergoing IVF. Non-POSEIDON women have almost 2-fold higher CLBR in comparison to POSEIDON group. With at least one embryo transfer done, young POSEIDON women have similar cumulative live birth rate (CLBR) as non-POSEIDON women. Similarly, with at least one embryo transfer done, women's CLBR in POSEIDON suboptimal response group 1b and group 2b was nearer to normo-responders. This implies that the age and oocyte quantity are the independent factors affecting CLBR in both POSEIDON and non-POSEIDON groups. POSEIDON stratification of low prognosis women undergoing IVF may help the clinicians to individualize the treatment protocols, select the option of repeat IVF using self-oocyte, or refer the couple for IVF using donor oocyte. The same may be used in routine clinical practice to counsel the couples planning for IVF treatments. As most of the studies are retrospective on POSEIDON stratification and IVF outcomes, further prospective trials with larger sample size are warranted in different ethnic populations.

Conflict of Interest

Authors declare no conflict of interest.

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Supplementary Table

Supplementary table 1. Comparison of younger POSEIDON group with older POSEIDON group

Parameters	Group A	Group B	p-value
	POSEIDON 1 and 3 (<35 years)	POSEIDON 2 and 4 (≥ 35 years)	
Total rFSH*(IU)	2801.63±1093	3147.08±1354.85	<0.001
Total HMG# (IU)	600 (300,1875)	900 (375,3000)	<0.001
Oocytes retrieved #	6 (4,8)	5 (3,7)	<0.001
MII oocytes #	4 (3,5)	3 (2,5)	<0.001
Fertilization rate * (%)	96.71±16.99	93.39±24.18	<0.001
Cleavage rate # (%)	85.71 (0,100)	80 (0,100)	0.02
Total embryos #	4 (2,5)	3 (2,4)	<0.001
Vitrified embryos n (%)	253 (16.56)	79 (13.98)	0.152
Total pregnancy rate	25.55	16.75	<0.001
Clinical pregnancy rate	23.94	15.48	<0.001
Cumulative live birth rate	19.09	12.56	<0001

Supplementary table 2. Comparison of good ovarian reserve POSEIDON group with poor ovarian reserve POSEIDON group

Parameters	Group A	Group B	p-value
	POSEIDON 1 and 2	POSEIDON 3 and 4	
Total rFSH *	2875.47±1156.19	3123.96±1430.50	0.024
Total HMG #	600 (375,2250)	1425 (600,3150)	<0.001
Oocytes retrieved #	6 (4,7)	5 (3,7)	0.197
MII oocytes #	4 (2,5)	3 (2,5)	0.166
Fertilization rate #	96.13±18.45	93.65±24.30	0.39
Cleavage rate #	83.33 (0,100)	100 (66.66,100)	<0.001
Total embryos #	4 (2,5)	3 (2,5)	0.105
Vitrified embryos n (%)	308 (15.72)	24 (17.91)	0.502
Total pregnancy rate	23.41	19.84	0.393
Clinical pregnancy rate	21.83	19.08	0.512
Cumulative live birth rate	17.53	14.50	0.817

* Mean ± SD, #Median (interquartile range)

Supplementary table 3. Success probability of live birth in POSEIDON and non-POSEIDON groups (normo- responder and hyper-responder) according to number of embryo transfers

Time	Total	Live birth	Success rate (%)	Failure	95% confidence interval
Group 1a					
1 ET	197	22	11	0.89	0.84-0.93
2 ET	1	0	11	0.89	0.84-0.93
Group 1b					
1 ET	1090	208	19	0.81	0.78-0.83
2 ET	123	35	42	0.58	0.51-0.64
3 ET	14	6	67	0.33	0.18-0.48
Group 2a					
1 ET	92	8	9	0.91	0.83-0.96
Group 2b					
1 ET	344	48	14	0.86	0.82-0.89
2 ET	34	6	29	0.71	0.58-0.81
3 ET	2	1	65	0.35	0.02-0.76
Group 3					
1 ET	69	9	13	0.87	0.76-0.93
2 ET	13	2	26	0.74	0.50-0.87
3 ET	2	2	100	0.00	.
Group 4					
1 ET	47	6	13	0.87	0.74-0.9
2 ET	4	0	13	0.87	0.74-0.94
Group 5 (normo-responder)					
1 ET	1140	190	17	0.83	0.81-0.85
2 ET	495	182	47	0.53	0.49-0.56
3 ET	83	22	61	0.39	0.33-0.44
4 ET	4	0	61	0.39	0.33-0.44
Group 6 (hyper-responder)					
1 ET	99	23	23	0.77	0.67-0.84
2 ET	65	28	56	0.44	0.33-0.54
3 ET	22	6	68	0.32	0.21-0.43
4 ET	4	0	68	0.32	0.21-0.43

Supplementary table 4. Success probability of live birth in POSEIDON and non-POSEIDON (combined sub-groups) according to number of embryo transfer

Time	Total	Live birth	Success rate (%)	Failure function	95% confidence interval
POSEIDON group					
1 ET	1839	301	16	0.84	0.82-0.85
2 ET	175	43	37	0.63	0.57-0.68
3 ET	18	9	68	0.32	0.17-0.46
Non-POSEIDON group					
1 ET	1239	213	17	0.83	0.81-0.85
2 ET	560	210	48	0.52	0.48-0.55
3 ET	105	28	61	0.39	0.33-0.43
4 ET	8	0	61	0.39	0.33-0.43

Supplementary table 5. Success probability of live birth in POSEIDON and non-POSEIDON groups (age wise distribution; <35 years, ≥ 35 years) according to number of embryo transfers

Time	Total	Live birth	Success rate (%)	Failure	95% confidence interval
Younger POSEIDON group					
1 ET	1356	239	18	0.82	0.80-0.84
2 ET	137	37	40	0.60	0.53-0.66
3 ET	16	8	70	0.30	0.16-0.45
Older POSEIDON group					
1 ET	483	62	13	0.87	0.84-0.90
2 ET	38	6	27	0.73	0.61-0.82
3 ET	2	1	63	0.37	0.01-0.78
Younger non-POSEIDON group					
1 ET	1047	186	18	0.82	0.80-0.84
2 ET	474	186	50	0.50	0.46-0.53
3 ET	88	25	64	0.36	0.30-0.41
4 ET	8	0	64	0.36	0.30-0.41
Older non-POSEIDON group					
1 ET	192	27	14	0.86	0.80-0.90
2 ET	86	24	38	0.62	0.52-0.70
3 ET	17	3	49	0.51	0.37-0.63