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Article

The prognosis of sub group of unexpected poor responders (POSEIDON group 1) in a cohort of normal responder women; is it really poor?

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Abstract. *Background*: Poor responders still represent one of the most challenging patients in fertility practice. Recently "*Patient Oriented Strategies Encompassing IndividualizeD Oocyte Number*" classification of suboptimal/poor responders, considering essential characteristics of infertile women, which could have a pivotal impact on the outcome of ICSI cycles in those women. *Objective*: the aim was to compare the clinical & ongoing pregnancy rates between normal responder women and POSEIDON group 1 women in GnRH antagonist ICSI cycles. *Methods:* observational prospective cohort study conducted for 350 women with normal ovarian reserve and aged < 35 years; GnRH antagonist protocol was used for all women. The primary outcomes were clinical and ongoing pregnancy rate. *Results:* out of 350 women in the study, 42 women (12 %) were found to be unexpected suboptimal/poor response. there was a statistically significant difference regarding age, body mass index, antral follicles count, anti-mullerian hormone level, total FSH dose and number of follicles >11 mm on day of ovulation trigger. Group of normal

responders (308/350) have more oocytes retrieved than POSEIDON group 1 however, there was no statistically significant difference in clinical pregnancy (36.1 % vs. 51.2 %, p = 0.087) and ongoing pregnancy (36.1 % vs. 43.6 %, p = 0.392) rates between women in POSEIDON group 1 and normal responders women respectively. There were no women with miscarriages in POSEIDON group (all the clinically pregnant women continued their pregnancy beyond 12 weeks).*Conclusion:* it was concluded that poor responder women with good ovarian reserve and aged < 35 years would have a comparable pregnancy rates to normal responder women.

Keywords*:* poor responders, POSEIDON, antagonist protocol, clinical pregnancy rate, ongoing pregnancy rate.

Introduction & background

Poor responders in IVF/ICSI still represent one of the most challenging groups of patients in fertility practice. Yet, a major limitation of the available published research is the obvious heterogeneity in the defining criteria used to define a poor response, which could impair the validity of the results (1-3). The estimated prevalence of poor response in IVF/ICSI ranges from 6% to 35% (4, 5) the wide variable range resulted from the striking diversity in criteria used for definition & classification of poor responders.

Recently, a group of researchers "the POSEIDON group" proposed a more detailed "***Patient Oriented Strategies Encompassing IndividualizeD Oocyte Number***" classification of suboptimal/poor responders, considering essential characteristics of infertile women, which could have a pivotal impact on the outcome of ICSI cycles in those women.(6)

Therefore, stratification is not only relied on the number of oocytes retrieved, but also took into account various features that may affect reproductive outcomes and should be carefully taken into consideration, in the era of individualized ovarian stimulation, such as age and ovarian "sensitivity" to conventional ovarian stimulation.(6, 7)

The cumulative live birth rate was shown to be significantly lower in women with poor oocyte yield as compared with normal responders.(8)

The exact pathophysiology claimed for the unexpected poor response in POSEIDON group 1 is still not fully discovered. However the most plausible explanation would be the decreased sensitivity of follicles to exogenous FSH. It has been shown that polymorphisms of FSH receptor may be correlated to response to ovarian stimulation (9).

It was shown that the reason for good outcomes in POSEIDON group 1 is the younger age of the women (compared to other POSEIDON categories) which is associated with lower oocyte and embryo aneuploidy rates.

There is no clear evidence for the best management for POSEIDON group 1 but increasing rec-FSH dose, addition of rec-LH together with rec-FSH and using DuoStim protocol (10, 11) have been considered for management of those women.(12)

The prognosis of sub group of unexpected poor responders (POSEIDON group 1) in a cohort of normal responder women

Objective

The present study was conducted aimed at comparing the clinical and ongoing pregnancy rates between normal responder women and POSEIDON group (1) women in GnRH antagonist ICSI cycles.

Methods

Study design, setting and participants

The present study was an observational prospective cohort study performed in the period from December 2019 to December 2020 performed in University Hospital IVF center and a private IVF center in Alexandria, Egypt. The Institutional ethical review board approved the study protocol and informed written consent was obtained from all participants after discussing the nature of the study. Women aged < 35 years with expected normal response to standard COS (according to antral follicle count "AFC" and anti-mullerian hormone "AMH" level); AMH ranged 1.2 – 4 ng/dl and AFC ≥ 5, attending for ICSI for various indications were enrolled in the study. Women underwent screening phase of the study included history taking (, and physical examination including a pelvic examination. Laboratory investigations (serum E2, LH, FSH, AMH, and PRL) and TVUS were performed on day 2 of the starting cycle. Semen of the male partners was assessed by CASA for all the couples.

Exclusion criteria: women with PCOS, women with history of OHSS in previous ICSI cycle, women with history of poor ovarian response, women with suboptimal ovarian reserve testing (AFC & AMH level), azoospermic males also were excluded.

Sample size calculation was performed for the primary outcome
of the study (Clinical and ongoing pregnancy rate) but there were no previous similar studies comparing normal responders and POSEIDON group 1 so, calculation was based on studies comparing normal responders and poor responders as a whole group.

Controlled ovarian stimulation: GnRH antagonist protocol was used in all women in the study. All patients received a daily dose (150–300 IU according to age, BMI, AFC and AMH level) of Rec-FSH; follitropin alfa (Gonal-F; Merck Serono Europe Ltd, London, UK) started from 2nd day of the menstrual cycle (whether natural or induced) for 5 days.

Starting on day 5 of stimulation, patients underwent monitoring with transvaginal ultrasound for evaluation of the thickness & pattern of the endometrium and the size & number of the growing follicles and serial assessment of oestradiol level every 2–3 days as required.

"Fixed antagonist protocol" was used to inhibit premature LH surge, a daily subcutaneous dose of 0.25 mg of GnRH antagonist cetrorelix (Cetrotide; Merck Serono Europe Ltd, London, UK) was initiated on day 6 of ovarian stimulation regardless of the size of the dominant follicle and continued up to day of administration of hCG.

Women were followed till three leading follicles reach 17 mm or more in size (13) , then serum progesterone level & E2 level were tested and a bolus of 250 μg of recombinant HCG (14) (Ovitrelle, Merck Serono Europe Ltd, London, UK) was administrated to trigger final oocyte maturation.

Ultrasound guided transvaginal oocyte retrieval was performed after 36 – 37 hours form administration of the triggering bolus.

Embryo transfer (ET) was performed either on day 2/3 (cleavage stage) or day 5/6 (blastocyst transfer) according to availability of embryos. Excess embryos of excellent quality were vitrified.

Follow up: Two weeks after ET, a serum beta-hCG level was determined for all patients, women with positive pregnancy test underwent transvaginal ultrasound (after approximately 4 weeks of ET) for diagnosis of a clinical pregnancy. Clinically pregnant women were followed till 14 weeks of pregnancy to estimate ongoing pregnancy rate.

Outcome measures: the primary outcomes of the study were the clinical pregnancy rate (calculated by considering clinical pregnancy, determined by the visualization of a viable gestational sac within the uterine cavity by ultrasound 3– 4 weeks after embryo transfer), Ongoing pregnancy rate (defined as pregnancy progressing beyond 12 weeks gestation).

Statistical analysis: data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). For analysis, $p < 0.05$ was considered to be significant.

The used tests were:

1 - Chi-square test

For categorical variables, to compare between different groups

2 - Student t-test

For normally distributed quantitative variables, to compare between two studied groups

3 - Mann Whitney test

For abnormally distributed quantitative variables, to compare between two studied groups

The prognosis of sub group of unexpected poor responders (POSEIDON group 1) in a cohort of normal responder women

Results

The study population was 350 women with expected normal ovarian response. After oocyte retrieval, women were divided into two groups according to response to COS i.e. number of oocytes retrieved; group 1 (Normal responders; retrieval of ≥ 10 oocytes) and group 2 (Poor responder "POSEIDON 1"; retrieval of < 10 oocytes) despite of apparently good prognosis criteria (age < 35 years, AFC >5 and AMH ≥1.2) following the conventional ovarian stimulation used.

Group 1 included 308 women (88 % of the sample) out of them 289 women underwent fresh ET and 19 women treated with freeze all embryos and subsequent FET (frozen embryo transfer).

Group 2 included 42 women (12 % of the sample) out of them 36 women underwent fresh ET and in the remaining 6 women ET was cancelled due to lack of embryos at day 3.

When comparing the group of normal responders with the group of poor responders (table 1); there was a statistically significant difference regarding age, BMI, AFC, AMH level, total FSH dose and number of follicles >11 mm on day of ovulation trigger.

Comparing the two groups regarding number of oocyte retrieved; there were statistically significant fewer oocytes retrieved and also fewer mature oocytes numbers in the group of POSEIDON 1. However, there was no statistically significant difference between the two groups concerning MII percentage (**Table 1**).

Table (1): Comparison between characteristics of Normal responders and POSEIDON group 1

Parameter	POSEIDON 1 (n = 42)	Normal responders (n = 308)	Test of significance	p
Mean age (years) ± SD.	32.93 ± 3.14	29.86 ± 3.87	t=5.761*	<0.001*
Mean BMI (kg/m²) ± SD	26.76 ± 2.53	27.78 ± 2.83	t=-2.211*	0.028*
Mean AFC ± SD	11.9 ± 3.55	16.15 ± 3.56	t=7.261*	<0.001*
Median AMH level ng/dl (min – max)	1.36 (1.11 – 3.90)	2.34 (1.1 – 4)	U=2479.0*	<0.001*
Median total FSH dose IU (min – max)	4000 (1350 – 4800)	1600 (1200 – 4600)	U=989.5*	<0.001*
Median no. of follicles ≥ 11 mm on day of trigger	9.50 (5 –13)	16 (6 – 40)	U=678.50*	<0.001*
Median number of retrieved oocytes (min- max)	5 (2 – 9)	15 (5 – 51)	U = 181.50*	<0.001*
Median number of MII oocytes (min-max)	3 (1 – 7)	11 (1 – 36)	U = 456.50*	<0.001*
Mean MII oocytes percentage ± SD	72.99 ± 21.66	77.29 ± 17.16	t=1.237	0.222

U: Mann Whitney test **t: Student t-test**

p: p value for comparing between **the two categories**

*: Statistically significant at p ≤ 0.05

Figure 1 shows that there was no statistically significant difference in clinical pregnancy (36.1 % vs. 51.2 %, p = 0.087) and ongoing pregnancy (36.1 % vs. 43.6 %, p = 0.392) rates between normal responders and POSEIDON group 1 respectively. There were no women with miscarriages in POSEIDON group (all the clinically pregnant women continued their pregnancy beyond 12 weeks).

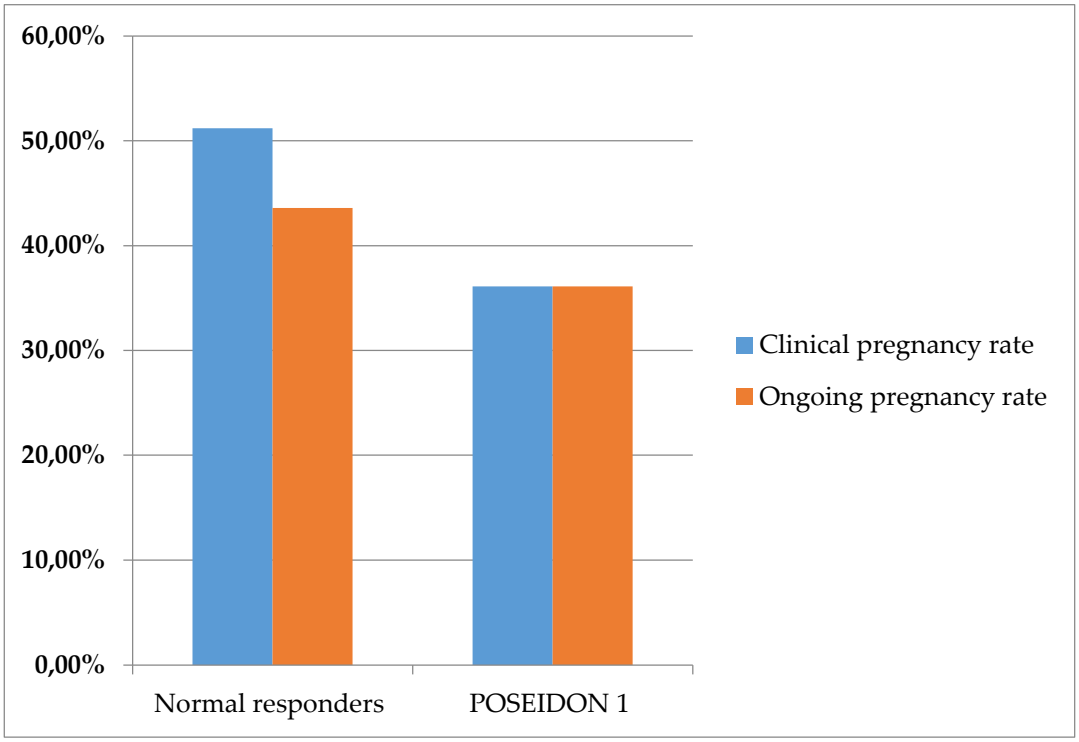

Figure (1): CPR and OPR in normal and POSEIDON 1 groups.

For the group of poor responders (POSEIDON 1) n = 36 women (who underwent fresh ET),women with clinical & ongoing pregnancy in this group had statistically more oocytes retrieved than non – pregnant women (5.26 ± 1.84 vs. 4.15 ± 1.07, p = 0.048). However, there was no significant difference between pregnant and non- pregnant women in POSEIDON 1 group according to number of mature oocytes (p = 0.0181), fertilization rate (p = 0.23) and blastocyst rate (p = 0.511).

Discussion

It has been recently proposed that suboptimal response to stimulation significantly jeopardizes success outcomes of ICSI and that women with unexpected poor/suboptimal responders may have better prognosis compared to patients with predicted low response, it could be stated that

POSEIDON group 1 patients may represent the most interesting group, on which clinical research should focus in the future.(1)

Since the first description of POSEIDON criteria (6) for definition & classification of poor responder women, POSEIDON group 1 women have gained specific attention as they are "unexpected" or "subtle" low prognosis patients with young age and apparently good ovarian reserve testing (AMH ≥ 1.2 ng/dl & AMH > 5 follicles) (6).

The present study is one of very few studies to date comparing between outcomes of IVF/ICSI in normal responders and specifically the group of recently described as unexpected poor responders (POSEIDON 1 group).

This study reported significantly fewer numbers of oocytes retrieved & MII oocytes numbers in POSEIDON group 1 women as compared to normal responders women. But there was no difference between the two groups in CPR and OPR. There was an interesting finding that there were no cases of miscarriage in POSEIDON 1 group (all the clinically pregnant women continued their pregnancy beyond 12 weeks).

In six women (6/42) of the POSEIDON 1 group, we had to cancel ET due to poor fertilization & subsequent embryo division on day 3 post ET which is expected in this specific subgroup (number of retrieved oocytes in all of them was < 3 oocytes). However the remaining women of POSEIDON 1 group showed a comparable CPR & OPR to the group of optimal ovarian response.

It appears that age of the woman remains the single most strong predictor of oocyte number and hence the success of IVF/ICSI. In our patients although all of them were aged less than 35 years yet, women in POSEIDON group 1 were statistically significant older than normal responder women (32.93 ± 3.14 vs. 29.86 ± 3.87 respectively, $p < 0.001$) this is consistent with the published literature in this issue.(15)

This study is considered the first study to address the differences in outcomes between normal responders and POSEIDON subgroup 1 specifically. However there are few studies comparing POSEIDON group 1 with other groups in POSEIDON classification.

In the study of Eftekhar et al. (2018) (16), they retrospectively analyzed outcomes of IVF/ICSI cycles in 245 poor responder women classified according to novel POSEIDON categories. Out of total women in this study forty one women were classified as POSEIDON subgroup 1, those women were shown to have significantly lower total FSH dose used, significantly higher number of COCs retrieved, significantly more mature oocytes (MII) than women in other POSEIDON subgroups. Regarding IVF success parameters, fertilization and implantation rate were comparable between groups ($p > 0.05$) but chemical pregnancy, clinical pregnancy and LBR were significantly higher in POSEIDON subgroups 1 & 2 as compared with subgroups 3 & 4.

However, when comparing outcomes in POSEIDON subgroup 1 and subgroup 2, there were no statistically significant differences in fertilization, implantation, chemical pregnancy, clinical pregnancy and LBR.

Additionally, Seven and colleagues (2020) (17) conducted a retrospective study for 276 poor responders women categorized through POSEIDON criteria. There were (134/276) women in POSEIDON subgroup 1. The number of oocytes retrieved the number of mature oocytes and the number of viable embryos was higher in the unexpected POR groups. But the number and the rate of mature oocyte and the fertilization rate did not differ in four POSEIDON groups. Implantation rate, clinical pregnancy rate, and miscarriage rate, which are the qualitative markers

of cycles, were similar among the four groups. LBR was statistically higher in unexpected POR groups.

Our study has the advantages of being a prospective study comparing women with normal response and women with unexpected poor response to ovarian stimulation and enrolled a relatively large sample size. However the study ended when an ongoing pregnancy (at least 12 weeks gestation) is achieved and follow up for a live birth or take home baby was not done. We also did not include in the study the evolving method for ovulation triggering in antagonist cycles (GnRH agonist) which have been shown to be associated with a comparable oocyte retrieval rate & MII oocytes percentage especially in poor responders women.
Further interventional researches and RCTs should be conducted to explore the overlooked group of unexpected poor responder, their management strategies and prognosis

Conclusion

From the present study we can conclude that poor responder women with good ovarian reserve and aged < 35 years would have a comparable pregnancy rates to normal responder women and this probably due to their young age's low aneuploidy rates in oocytes/embryos.

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Conflict of interest

None

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