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Research Article

Women's Age is the Best Success Predictor in a Cohort of Poor Responders: A Retrospective analysis according to POSEIDON Criteria

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- Controlled ovarian stimulation
- Poor ovarian response
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Abstract

Introduction: Currently there is great interest in analyzing patients with poor response to determine cycle outcomes in a way to develop new treatment strategies for this group of patients.

Purpose: To classify a cohort of infertile patients according to Poseidon criteria and compare groups demographic profile and cycle outcomes.

Method: An observational, retrospective study, based on 558 assisted reproduction cycles performed between 2015 and 2018 at a single quaternary center in Brazil. Group division was according to Poseidon's criteria. Groups 1 and 2 included patients with AFC ≥ 5 and ≤ 9 oocytes retrieved in a previous cycle. Younger patients (age < 35y) were included in Group 1, while older patients (age ≥ 35y) were included in Group 2. These groups were subdivided into groups 1A (<35y, <4 oocytes), 1B (<35y, 4-9 oocytes), 2A (≥ 35y, < 4 oocytes), and 2B (≥35y, 4-9 oocytes). The groups 3 (<35y) and 4 (≥ 35y) consisted of patients with AFC lower than 5. Comparisons were made between the subgroups and relative to a control group of patients who retrieved ≥ 10 oocytes, being then subdivided in patients younger than 35 years (C1) and over 35 years (C2).

Results: Groups 1B and C1 had a higher rate of clinical pregnancy (p=0,028), Groups 3, 4 and 2A of Poseidon had less oocytes recovered (p < 0,001). Group 4 had a smaller number of embryos formed (p=0,001).

Conclusion: Woman's age, more than the ovarian reserve, is the main determinant of success in poor prognosis patients.

INTRODUCTION

The relationship between the number of eggs retrieved in an ovarian stimulation cycle and live birth suggests that the number of eggs in IVF is a robust surrogate outcome for clinical success [1]. However, there are patients who do not respond adequately to stimulation, constituting the poor ovarian response (POR) group.

The incidence of inadequate response to ovarian stimulation is estimated to be between 9% and 24% [2-4]. It is difficult to assess outcomes and to propose treatments for this population due to the discrepancies in the diagnostic criteria adopted by the studies [5].

In 2011, a group of experts from the European Society of Human Reproduction and Embryology (ESHRE) met in Bologna, Italy, to develop diagnostic criteria for POR based on the evidence available at the time [6]. The live birth rate after conventional ovarian stimulation was similarly low in three unrelated studies conducted by the Bologna group [7-9], corroborating the validity of the criteria. However, critics emerged referring mainly to the heterogenicity of the patients subclassified according to the Bologna criteria. In addition, remarks were made regarding the lack of evaluation of oocyte quality, the cut-off values established for age and ovarian response tests, and the absence of discrimination among all risk factors for POR [10-14].

Recently, in an effort to further refine the Bologna criteria, the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) was proposed. These criteria stratify

patients according to age, ovarian biomarkers, and ovarian response if a previous stimulation has been performed [15].

That different groups of POSEIDON have indeed a poor prognosis and are distinct from each other gives validity to this new classification. Additionally, a description and a comparison of group behavior would help determine risk factors and explain differences in treatment and in clinical outcomes, leading to more objective and targeted reproductive medicine.

the present study, we retrospectively applied the POSEIDON stratification to patients who underwent IVF/ICSI treatment to better determine cycle outcomes in each group, including live birth rate per cycle initiated, in a real-world setting.

MATERIALS AND METHODS

Study Design and Patients

This is a retrospective cohort of women who underwent ART at the Centro de Reprodução Humana, Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (HCFMUSP), between January 2015 and December 2018. Women aged 18 years or older who underwent IVF/ICSI were included. The exclusion criteria were (1) infectious-contagious diseases or medical conditions that contraindicated pregnancy due to the high risk involved, (2) BMI below 18 kg/m2 or above 30 kg/m2, and (3) absence of data regarding the patient's age, antral follicle count (AFC), and number of oocytes recovered, making it impossible to stratify the patient according to the POSEIDON groups.

The present study protocol was analyzed and approved by the Ethics Committee of the Departamento de Obstetrícia e Ginecologia, HCFMUSP.

POSEIDON Stratification

The POSEIDON stratification was applied retrospectively to the patients based on the age when the patients received their ART treatment and the number of oocytes retrieved during the first stimulation cycle [15].

The POSEIDON groups 1 and 2 included patients with AFC equal to 5 or more and 9 or more oocytes retrieved after standard ovarian stimulation. Younger patients (age < 35 years) were included in POSEIDON group 1, while older patients (age ≥ 35 years) were included in POSEIDON group 2. These groups were subdivided into groups 1A (<35y, <4 oocytes retrieved), 1B (<35y, 4-9 oocytes retrieved), 2A (≥ 35y, < 4 oocytes retrieved), and 2B (≥35y, 4-9 oocytes retrieved).

The POSEIDON groups 3 and 4 consisted of patients with AFC lower than 5. Younger patients (age < 35 years) were included in POSEIDON group 3, while older patients (age ≥ 35 years) were included in POSEIDON group 4.

Age-matched control groups with AFC equal to 5 or more and with no prior poor response were defined for comparative purposes. Group C1 comprised women younger than 35 years and group C2, women aged 35 or older.

In Vitro Fertilization Protocol

Briefly, pituitary blockage was obtained either with a GnRH agonist or a GnRH antagonist. Ovarian stimulation was accomplished using either recombinant follicle-stimulating hormone (FSHr), urinary follicle-stimulating hormone (FSHu), or menotropin (HMG) with doses varying from 150 to 300 IU per day. The gonadotropin doses were adjusted according to the ovarian response. When at least 2 follicles reached a diameter of 18 mm, follicular maturation was triggered with an injection of recombinant human chorionic gonadotropin (rhCG) or GnRH agonist. Oocyte retrieval was performed after 36 hours by transvaginal ultrasound-guided aspiration; the luteal phase was supported by daily micronized progesterone via the vaginal approach, starting on the day of oocyte retrieval. All oocytes were fertilized by intracytoplasmic sperm injection.

Embryos were cultured according to standard methods in a triple gas incubator (90% N2, 5% O2, and 6% CO2) at 37°C. Embryo transfers (ETs) were performed on day 3 (D3) or day 5 (D5) of development. The embryos on D3 were considered good quality when they presented with 8 to 10 symmetric blastomeres, no multinucleations, and a maximum fragmentation level of 20% [16]. Blastocysts on D5 of development were considered good quality when they were expanded (grades 3 or 4), the inner cell mass grades were A or B, and the trophectoderm was A or B [17].

For warming, a Vit Kit-Thaw (Irvine Scientific, USA) was used. For the frozen-thawed ETs, endometrial preparation was conducted with 2 mg of oral estradiol valerate 3 times a day. When trilaminar endometrium with 7 mm of thickness or more was observed on ultrasound, daily administration of 600 mg of vaginal micronized progesterone was initiated. The embryos were thawed, evaluated for survival, and then transferred to the uterine cavity after the patient had used progesterone for the number of days corresponding to the age of the embryo in days: 3 days of progesterone for cleavage and 5 days of progesterone for blastocysts.

The luteal phase support was maintained for all patients with daily 600 mg of micronized progesterone after embryo transfer and, for frozen-thawed transfer cycles, estradiol valerate was used concomitantly. Biochemical gestation was confirmed by measurement of βHCG 9 to 12 days after embryo transfer, and clinical pregnancy was confirmed by ultrasound with the presence of a gestational sac and heartbeat two weeks after detection of positive βHCG. Luteal phase support was maintained until completion of 12 weeks of gestational age.

Statistical Analysis

Initially, all variables were analyzed descriptively. For quantitative variables, the analysis was done by observing the relative and maximum values and calculating means, standard deviations, and quartiles. For qualitative variables, absolute and relative frequencies were calculated.

For comparing the groups in terms of quantitative variables, the analysis of variance by factor with the Bonferroni test was used. When the assumption of data normality was rejected, the Kruskal-Wallis nonparametric test and Dunn's test were used [18].

The homogeneity of the proportions was tested with the chi-square test or the maximum likelihood test [18].

The software used for the calculations was SPSS 17.0 for Windows. The level of significance used for the tests was 5%.

RESULTS

Initially, the sample consisted of 558 cycles of in vitro fertilization. The study groups were divided into 1A (n = 15), 1B (n = 19), 2A (n = 48), 2B (n = 59), 3 (n = 17), 4 (n = 50), C1 (n = 157), and C2 (n = 193) (Figure 1).

Women's ages in the 558 cycles ranged from 24 to 42 years and averaged 35.07 years (SD ± 3.69y). Men's ages ranged from 24 to 55 years and averaged 37.51 years (SD ± 6.09 years). The time span of the couples' infertility varied between 0.5 and 19 years and averaged 7.04 years (SD ± 3.84y).

The male factor was the most prevalent cause of infertility. A comparison of the groups reveals that group 3 and 4 had a significantly higher percentage of endometriosis, and groups 2A, 2B, and C2 had a significantly higher percentage of uterine factor (Table 1 and Table 2, Figure 2).

On the subject of controlled ovarian stimulation protocols, the highest percentage of cycles used GnRh antagonist for pituitary blockage (69.9%) and HMG (59.6%) for ovarian stimulation.

A comparison of the groups showed that group 2B had a significantly higher percentage of short agonist cycles than the other groups, and groups C2, 3, and 4 used more recombinant FSH than any other group. Groups 3 and 4 had a higher cancellation rate.

Of the total cycles, 445 (86.4%) were triggered with HCG and 72 (13.6%) with the GnRh agonist. Groups 2A, 2B, 3, and 4 showed a lower proportion of cycles with an agonist trigger (Table 3).

The total gonadotropin dose of group C1 was significantly lower than that of group 2B, and there were no differences between the other groups. Nor was there a significant difference in length of days of stimulation. Endometrial measurements and estradiol levels on the trigger day of group 4 were significantly lower than those of the other groups, except for group 3 (Table 4).

With respect to cycle outcomes, groups 3, 4, and 2A had a significantly lower number of recovered total eggs and mature

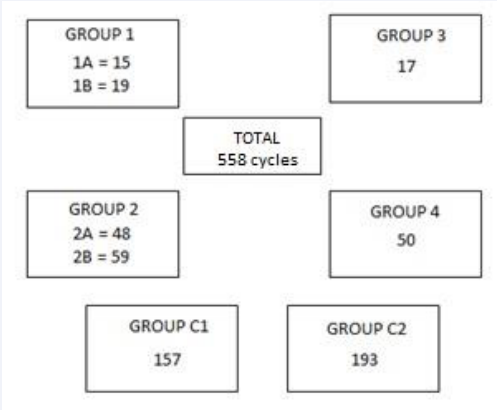

Figure 1 Distribution of the Study Groups.

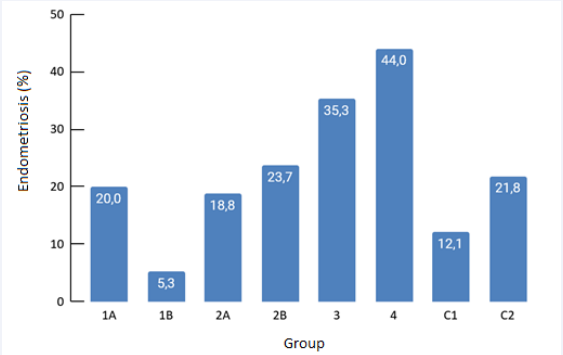

Figure 2 Prevalence of endometriosis as an infertility factor by study group.

Variable	1A n	1A %	1B n	1B %	2A n	2A %	2B n	2B %	3 n	3 %	4 n	4 %	C1 n	C1 %	C2 n	C2 %	p
Cause																	
Male factor	12	80.0	15	78.9	35	72.9	49	83.1	15	88.2	39	78.0	135	86.0	156	80.8	0.581[1]
Endometriosis	3	20.0	1	5.3	9	18.8	14	23.7	6	35.3	22	44.0	19	12.1	42	21.8	<0.001[1]
Uterine	1	6.7	2	10.5	14	29.2	14	23.7	0	0.0	9	18.0	16	10.2	56	29.0	<0.001[1]
Ovulatory disfunction	8	53.3	4	21.1	9	18.8	18	30.5	3	17.6	8	16.0	42	26.8	45	23.3	0.107[1]
Tubal	5	33.3	9	47.4	20	41.7	27	45.8	6	35.3	19	38.0	42	26.8	75	38.9	0.150[1]
Recurrent miscarriage	0	0.0	0	0.0	1	2.1	2	3.4	0	0.0	1	2.0	2	1.3	7	3.6	0.679[2]
Unexplained infertility	1	6.7	1	5.3	8	16.7	2	3.4	0	0.0	1	2.0	6	3.8	13	6.7	0.068[2]

(1) Descriptive probability level of the chi-square test (2) Descriptive probability level of the likelihood test.

Table 1 Infertility factors according to study groups.

Table 2: Absolute and relative frequencies of stimulation parameters.

		n	%
Type of cycle	Long agonist	155	28.0
	Short agonist	12	2.2
	Antagonist	387	69.9
Gonadotropin	FSHu	112	20.7
	FSHr	106	19.6
	HMG	322	59.6

Variable	1A n	1A %	1B n	1B %	2A n	2A %	2B n	2B %	3 n	3 %	4 n	4 %	C1 n	C1 %	C2 n	C2 %	p
Type of cycle																	0.044[2]
Long agonist	2	13.3	4	21.1	18	38.3	19	32.2	4	23.5	15	31.3	32	20.4	61	31.8	
Short agonist	0	0.0	0	0.0	0	0.0	4	6.8	0	0.0	1	2.1	1	0.6	6	3.1	
Antagonist	13	86.7	15	78.9	29	61.7	36	61.0	13	76.5	32	66.7	124	79.0	125	65.1	
Gonadotropin																	0.003[2]
FSHu	2	14.3	4	21.1	11	24.4	18	31.6	3	18.8	12	25.5	25	16.1	37	19.8	
FSHr	2	14.3	0	0.0	4	8.9	7	12.3	5	31.3	10	21.3	25	16.1	53	28.3	
HMG	10	71.4	15	78.9	30	66.7	32	56.1	8	50.0	25	53.2	105	67.7	97	51.9	
Trigger																	<0.001[2]
HCG	12	80.0	14	77.8	44	97.8	53	93.0	13	100.0	40	100.0	119	77.8	162	86.2	
GnRH agonist	3	20.0	4	22.2	1	2.2	4	7.0	0	0.0	0	0.0	34	22.2	26	13.8	
Canceled cycle	0	0.0	0	0.0	2	4.2	0	0.0	2	12.5	9	18.0	1	0.6	4	2.1	<0.001[2]

Table 3 Infertility factors according to study groups.

Descriptive level of probability of the chi-square test.

Table 4: Descriptive values of stimulation according to the study groups

	GROUP	N	MEAN	SD	MIN	MAX	P25	MEDIAN	P75	P*
Gonadotropin total dose	1A	15	2066.67	692.41	1200.00	3375.00	1350.00	2000.00	2625.00	0.022
	1B	18	1886.11	351.07	900.00	2500.00	1706.25	1912.50	2043.75	
	2A	44	2077.84	506.30	600.00	3150.00	1725.00	2025.00	2418.75	
	2B	57	2121.93	590.08	1350.00	4725.00	1650.00	2025.00	2487.50	
	3	17	2092.65	489.16	1350.00	3150.00	1725.00	2025.00	2250.00	
	4	45	2052.78	440.50	900.00	3200.00	1800.00	2000.00	2400.00	
	C1	150	1853.67	463.84	150.00	2925.00	1575.00	1800.00	2181.25	
	C2	184	1906.25	481.54	800.00	3600.00	1581.25	1912.50	2250.00	
Length of stimulation	1A	15	10.73	2.66	7.00	16.00	9.00	10.00	13.00	0.889
	1B	19	10.26	1.45	8.00	13.00	9.00	10.00	11.00	
	2A	46	10.22	2.18	7.00	15.00	8.00	10.00	12.00	
	2B	58	10.64	2.55	7.00	22.00	9.00	10.00	11.00	
	3	17	10.29	2.64	6.00	15.00	9.00	9.00	12.00	
	4	45	9.1	2.09	4.00	14.00	8.00	10.00	12.00	
	C1	153	10.41	1.71	7.00	17.00	9.00	10.00	12.00	
	C2	189	10.06	1.82	4.00	16.00	9.00	10.00	11.00	
Estradiol	1A	13	1896.36	1411.27	127.00	5308.00	911.85	1683.00	2362.00	<0.001
	1B	12	2651.04	2600.56	558.00	9879.00	1374.25	1545.50	3344.25	
	2A	36	1272.49	825.44	246.50	3860.00	599.25	1296.50	1664.25	
	2B	50	1587.65	1099.43	196.00	5782.00	937.05	1257.50	2001.50	
	3	11	1095.11	507.79	482.30	1856.00	727.00	916.00	1747.00	
	4	26	699.67	435.77	47.40	1705.00	385.75	635.60	1098.75	
	C1	132	2460.14	2243.14	71.90	15430.00	1180.00	1781.50	2866.75	
	C2	155	1864.59	1628.74	107.60	12968.00	845.00	1387.00	2301.00	
Endometrium	1A	15	10.97	2.37	7.00	16.00	9.60	10.00	13.00	<0.001
	1B	19	10.88	2.08	7.00	16.00	10.00	10.00	13.00	
	2A	42	10.54	3.16	4.50	23.00	8.50	10.00	12.00	
	2B	58	10.42	2.96	5.00	24.00	9.00	10.00	12.00	
	3	14	9.51	1.68	7.00	13.70	8.75	9.75	10.00	
	4	40	8.52	2.41	3.00	14.00	7.00	9.00	9.85	
	C1	151	10.59	2.37	4.50	19.00	9.00	10.50	12.00	
	C2	184	10.46	2.73	5.00	20.00	8.50	10.00	12.00	

(*) Descriptive level of probability of the Kruskal-Wallis nonparametric test.

eggs than the control groups. Regarding the number of embryos which were formed, group 4 had a significantly lower number than groups 2B and C1 (Table 5).

The groups did not significantly differ in terms of the number of embryos transferred or the day of transfer. Groups 1A, 2B, C1, and C2 had a higher percentage of frozen embryos (Table 6).

When analyzing the clinical pregnancy rate (CPR) per fresh transfer, no difference between the groups was observed. However, when assessing CPR per started cycle (fresh transfers plus frozen embryo transfers), groups 1B and C1 had higher percentages than the other groups. There was no significant difference in live birth rates (LBR) between groups (Table 7).

When evaluating the relationship between LBR, woman's age, and AFC, we found that cycles with live births differed significantly from woman's age but not from AFC (Figure 3 and Figure 4).

DISCUSSION

The management of low prognosis patients remains a challenge for reproductive medicine practitioners.

Leijdekkers et al., in 2019 evaluated 551 patients with poor prognosis classified according to POSEIDON, with the main outcome being the cumulative rate of live births per patient over 18 months of treatment, including the multiple cycles initiated [16]. In their analysis, the authors found that, unlike the advanced age groups, the groups of young patients with an unexpected bad response in the first cycle did not differ from the control group over time. Thus, the study concludes that oocyte quality determined by maternal age is more relevant than number of eggs and that this outcome, in turn, would not have a relevant impact on the group of young patients [19]. Similarly, Abdullah et al., in 2020 evaluated the cumulative rate of live births of 461 patients in up to 3 treatment cycles, totaling 825 IVF cycles. Groups 1 and 3, composed of young patients, showed

Table 5: Descriptive values of the number of oocytes retrieved and maturity rates according to the study groups

	GROUP	N	MEAN	SD	MIN	MAX	P25	MEDIAN	P75	P*
Oocytes retrieved	1A	15	9.47	10.00	0.00	35.00	2.00	5.00	16.00	<0.001
	1B	19	8.42	5.11	3.00	18.00	4.00	7.00	12.00	
	2A	46	4.22	2.81	0.00	13.00	2.00	3.50	6.00	
	2B	59	7.03	4.86	0.00	22.00	4.00	6.00	9.00	
	3	14	4.00	3.37	0.00	13.00	2.00	3.00	6.00	
	4	41	2.98	2.33	0.00	10.00	1.00	2.00	5.00	
	C1	156	10.99	8.31	0.00	48.00	5.00	9.00	14.75	
	C2	189	8.76	7.16	0.00	45.00	4.00	7.00	12.00	
M2	1A	14	7.14	8.96	0.00	30.00	1.00	3.00	10.50	<0.001
	1B	19	6.53	4.15	2.00	14.00	3.00	5.00	9.00	
	2A	46	3.33	2.22	0.00	13.00	2.00	3.00	5.00	
	2B	56	5.70	3.85	0.00	17.00	3.00	4.00	8.00	
	3	14	2.93	2.53	0.00	9.00	1.00	2.00	4.50	
	4	41	2.41	2.00	0.00	8.00	1.00	2.00	4.00	
	C1	156	8.67	6.56	0.00	33.00	4.00	7.00	13.00	
	C2	189	6.78	5.34	0.00	32.00	3.00	6.00	9.00	
Embryos formed	1A	15	3.33	3.77	0.00	12.00	1.00	2.00	4.00	0.001
	1B	19	2.74	2.00	0.00	8.00	2.00	2.00	4.00	
	2A	46	1.93	1.37	0.00	6.00	1.00	2.00	2.00	
	2B	57	2.74	1.71	0.00	8.00	2.00	2.00	4.00	
	3	14	1.86	1.29	0.00	4.00	1.00	2.00	3.00	
	4	39	1.64	1.27	0.00	6.00	1.00	2.00	2.00	
	C1	156	3.32	2.59	0.00	10.00	2.00	2.00	5.00	
	C2	185	2.65	2.03	0.00	11.00	1.50	2.00	3.00	

(*) Descriptive level of probability of the Kruskal-Wallis nonparametric test.

Table 6: Absolute and relative frequencies of the number of embryos transferred, day of transfer, and presence of frozen embryos per study group

	Group																
	1A		1B		2A		2B		3		4		C1		C2		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	p
Transferred embryos																	0.099(1)
0	5	33.3	6	31.6	13	28.3	14	24.6	4	30.8	9	23.7	70	45.2	66	36.3	
1	3	20.0	1	5.3	9	19.6	4	7.0	3	23.1	11	28.9	16	10.3	27	14.8	
2	7	46.7	12	63.2	24	52.2	38	66.7	6	46.2	18	47.4	69	44.5	89	48.9	
3	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	
Transfer day																	0.207(1)
2	0	0.0	0	0.0	3	8.6	0	0.0	0	0.0	1	3.4	2	2.4	1	0.9	
3	3	30.0	7	63.6	23	65.7	27	62.8	6	60.0	21	72.4	45	53.6	71	60.7	
5	7	70.0	4	36.4	9	25.7	16	37.2	4	40.0	7	24.1	37	44.0	45	38.5	
Frozen embryos	7	53.8	6	31.6	11	28.2	27	52.9	5	45.5	9	28.1	80	55.9	95	56.9	0.002(1)

(1) Descriptive level of probability of the likelihood test.

Table 7: Absolute and relative frequencies of variables assessed according to the study groups

	Group																
	1A		1B		2A		2B		3		4		C1		C2		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	p
CPR per fresh transfer	1	10.0	2	15.4	4	11.8	8	18.6	3	30.0	4	15.4	23	26.7	29	25.0	0.502(1)
CPR per started cycle	3	20.0	5	31.3	4	9.5	9	18.0	3	20.0	5	13.2	45	33.6	45	25.9	0.028(1)
LBR	3	20.0	4	26.7	3	7.3	6	12.5	2	14.3	5	13.2	27	22.9	31	18.5	0.361(2)

(1) Descriptive level of probability of the chi-square test; (2) Descriptive level of likelihood test.

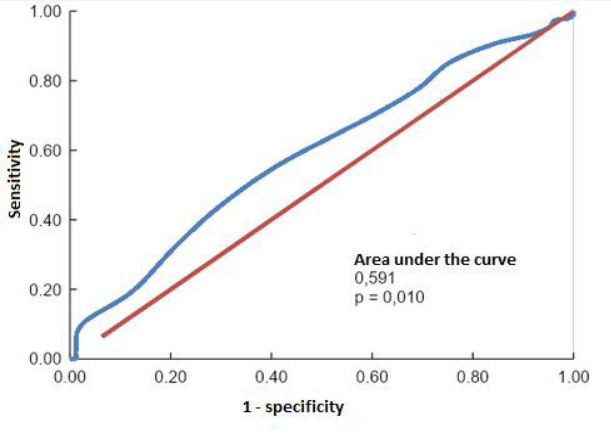

Figure 3 ROC curve - Woman's age vs. Live birth rate.

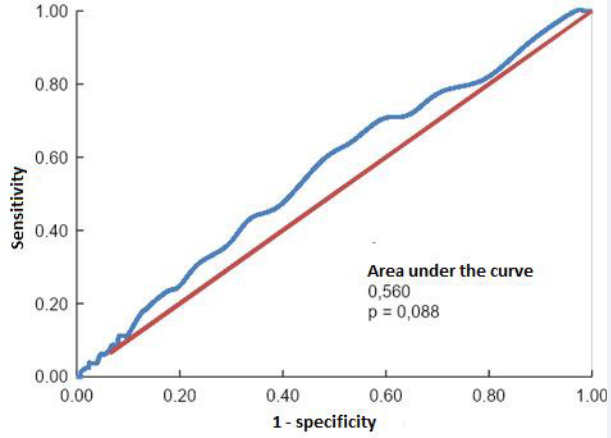

Figure 4 ROC curve – Antral follicle count vs. Live birth rate.

a good chance of having live births at the end of 3 cycles (77% and 51% respectively). On the other hand, group 4 had the worst prognosis, totaling a cumulative rate of live births of 22.34% at the end of 3 cycles [20].

The POSEIDON group released a statement saying that the preferred way of comparing groups would be to evaluate cumulative live births rates per started cycle as described by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and Organization World Health Organization (WHO) [21,22]. By definition, ICMART considers "cumulative birth rate with at least one live birth" as "the number of deliveries with at least one live birth resulting from an 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" [22].

Recent cohort studies have explored this outcome per started cycle, noting a significant difference between POSEIDON groups when compared to a control group. Li et al., in 2019 retrospectively evaluated 26,697 cycles of IVF, observing in POSEIDON groups 1, 2, 3 and 4 a cumulative live birth rate per cycle of 56.04%, 30.85%, 14.73%, and 6.58%, respectively. The study concluded that low ovarian reserve is a determining factor for low prognosis [23]. Shi et al., in 2019 retrospectively assessed 18,455 cycles of IVF comparing the POSEIDON groups with each other and with a control group. In this study, the POSEIDON groups 1, 2, 3, and 4 had a live birth rate of 44.6%, 24.5%, 35.5%, and 12.7%, respectively [24].

In the present study we compared the results of live births per initiated cycle, instead of the cumulative live birth rate of multiple treatment cycles over a given period of time or the cumulative live birth rate considering only cycles with embryo formation, excluding cancellations.

We believe that such an outcome is the one that best relates to clinical practice in countries where treatment is limited due to financial issues. In our country there are private clinics, in which IVF treatment is entirely financed by the couple, and public services, funded by the government, such as CRH-HCFMUSP, where budget restrictions impose a limit on the number of attempts per couple. In this scenario the result of a single cycle is more relevant than assessing accumulated results of more than one cycle. In many cases, the couple won't have the chance for another attempt.

That this study is a retrospective analysis is a limitation. On the other hand, the study has great external validity, for it simulates what actually occurs in clinical practice. As already expected, the groups were not homogeneous with respect to certain factors, such as the higher number of endometriosis cases in the low ovarian reserve groups (3 and 4). In all groups most cycles used the GnRH antagonist for pituitary blockage, HMG for ovarian stimulation, and HCG to trigger oocyte maturation.

Although there were more patients using FSHr in groups C2, 3, and 4 than in other groups, it should be noted that, at the CRH HCFMUSP, the choice of gonadotropins was largely based on what was available for use at the time the cycle was performed and that options were random and without clinical significance. Also, no difference between groups was noted regarding the number of days of stimulation and gonadotropin dose was only lower in the young control group (C1) comparing to others.

This may reflect a prescription preference for higher doses in groups with poor prognosis, whether due to advanced age, previous history of poor response or low reserve.

As to intermediate outcomes, we found that a previous history of poor response in younger patients doesn't translate in a poor response in a second cycle, since there was no difference between groups 1A and 1B compared to group C1 regarding number of oocytes retrieved.

On the other hand, women with advanced age and low ovarian reserve (group 4) had the worst intermediate outcomes: more cancelled cycles, smallest endometrial measurement and estradiol levels on trigger day and fewer embryos formed.

The present study concludes that the patient's age is the

most relevant factor in a prognostic assessment at the start of an assisted reproduction cycle. Group 4 had the lowest number of eggs and embryos. Groups 2 and 4 had lower rates of CPR per started cycle and lower rates of live births, albeit with no statistical significance.

When tracing a ROC curve crossing age and live birth rate it is observed that there is a significant difference related to age, being 35-year-old the best cutoff point to be adopted. Such analysis is in agreement with POSEIDON criteria, as opposed to the old Bologna criteria that established the age of 40 years as a cutoff point.

All things considered; the study raises the suspicion that the most determinant factor in lower live birth rates is the woman's age.

CONCLUSION

The POSEIDON groups differ from one another. Young patients with a low response in a previous cycle (groups 1A and 1B) have clinical pregnancy rates per started cycle and live birth rates similar to those of the control group in a second cycle. Older patients (groups 2 and 4) have the worst prognosis.

A woman's age rather than her ovarian reserve is the main predictor of success in poor prognosis patients.

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