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ORIGINAL ARTICLE

What did change in poor ovarian responders according to Bologna criteria over the 5 years? A tertiary IVF center experience

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ABSTRACT

Objective: The objective of the study was to evaluate the changes in the prevalence, management strategies, and cycle outcomes of the cycle with the poor ovarian response (POR).

Material and Methods: This study was retrospectively designed. Poor responder infertile women who fulfilled Bologna criteria were included in the study. Data were obtained from medical records of infertile couples who underwent the intracytoplasmic sperm injection and embryo transfer program from January 2014 to December 2018.

Results: Totally 776 cycles with POR were evaluated. The changing trend in the prevalence of the cycle with POR was estimated by rejecting the null hypothesis that there is no linear trend in the proportion of poor cycles across years ($\chi^2(1)=9.28$, $p=0.002$). A linear increasing trend in the proportion of poor cycles in the 5 years was found. A linear increase in the prefer of the antagonist protocol was found ($\chi^2(1)=6.61$, $p=0.010$), whereas there was a linear decrease in the minimal stimulation protocol with Clomiphene Citrate ($\chi^2(1)=11.028$, $p<0.001$). An increase in the usage of recombinant follicle-stimulating hormone (rFSH)/human menopausal gonadotropin (HMG) together was found ($\chi^2(1)=76.28$, $p<0.001$), whereas there was a decrease in the usage of the only FSH or HMG ($\chi^2(1)=18.11$ $p<0.001$; $\chi^2(1)=18.62$, $p<0.001$). There was no change in the trend of cycle outcomes during 5 years period.

Conclusion: There is a clear increasing trend in the prevalence of cycles with POR over the 5 years. Ovarian stimulation protocols and choice of gonadotropins have shown a changing trend.

Keywords: Bologna criteria, intracytoplasmic sperm injection, ovarian stimulation protocols, poor ovarian response, prevalence, trend.

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INTRODUCTION

The first poor ovarian response (POR) definition was reported by Garcia et al.[1] A standardized definition of POR was established by the recent European Society of Human Reproduction and Embryology (ESHRE) Consensus Conference.[2] Additionally, the first internationally accepted definition of PORs was announced by the ESHRE consensus called as Bologna criteria, which has been used by Asian Researchers with 65% and Europeans with 49%.[3] It is followed by the POSEIDON criteria classifying infertility patients with "expected" or "unexpected" inappropriate ovarian response to exogenous gonadotropins.[4]

In the infertile women population, the reported prevalence of PORs has exponentially grown and markedly fluctuated between 5.6% and 35.1%.[5–8] Since the first description, several hundred researches have been published about POR and PORs.[9,10] Through the accumulation of data, PORs and the cycles with poor response to controlled ovarian stimulation (COS) are the most challenging issues in the field of fertility treatment. The troubles in this area could be sorted as heterogeneity of POR population, the uncertainty of single pathophysiology, low or absence of oocytes yield, high cycle cancellation rates, poor embryo quality, high implantation failure, and low pregnancy rates.[8,11–13] An increase in the infertile women population with decreased reproductive potential by aging, rise in the successful treatment expectation of patients by introducing newer technologies has also forced physicians.[14]

According to the latest data of the 2011–2015 National Survey of Family Growth on infertility released on Center for Disease Control and Prevention, more than 7 million women of the approximately 61 million women aged 15–44 years (12%) had admitted any infertility units and almost 7% of married women aged 15–44 years were unable to get pregnant after at least 12 consecutive months of trying to conceive.[15] In the different infertile women populations, there is a considerable changing trend in several aspects over the decades.[16] In this study, we focused on the poor responder infertile women's group that fulfilled Bologna criteria. Knowledge about the prevalence of cycle with POR and the novel trends in the treatment of cycle with POR is vital for the counseling and the managing of poor responder women in clinical practice. Furthermore, this knowledge offers to clinicians an opportunity to rearrange the medical sources and the facilities taking into account trends in the treatment protocol and its outcomes. In this study, we aimed to assess the changes in the POR cycle in terms of the prevalence, the management strategies, and the cycle outcomes over 5 years.

MATERIAL AND METHODS

This study was designed retrospectively and conducted at the Assisted Reproduction Unit of the Zeynep Kamil Women's and Children's Hospital, İstanbul, Türkiye. Data were obtained from medical records of infertile couples who implemented the intracytoplasmic sperm injection (ICSI) and an embryo transfer program from January 2014 to December 2018. Local ethics committee approval was obtained for the study (approval number: 05/06/2015-90). The study was conducted under the Declaration of Helsinki Principles.

In this study, approximately 5663 cycles of obtained medical records were evaluated. At first, cycles with initial gonadotropin dose above/and 300 IU were evaluated. Poor responder women were selected according to the Bologna criteria: (1) Age (≥40 years) or have any other risk factors; (2) a previous POR (cycle cancelled or ≤3 oocytes with conventional stimulation protocol), or (3) abnormal ovarian tests (antral follicle count (AFC) of <5–7 follicles or anti-Mullerian hormone (AMH) level of <0.5–1.1 ng/ml).[2] Infertile women corresponded to at least two of Bologna criteria were included in the study. Women with a male partner with azoospermia (no spermatozoa in the ejaculate) or severe oligozoospermia with a sperm count of <5.0 million/ml ejaculate fluid were excluded from the study. Finally, 776 cycles belong to 536 infertile women corresponding study criteria were included in the study.

All treatment protocols, that were used daily, highly purified human menopausal gonadotropin (HMG) (75 IU, Menopur, Ferring, Istanbul, Türkiye), recombinant follicle-stimulating hormone (rFSH) (450 IU, Gonal-F, Merck, Istanbul, Türkiye), or the combination of them, were performed as described previously.[17] When at least one follicle reached 17-mm in diameter or above, ovulation was triggered using recombinant human chorionic gonadotropin (rec-hCG) (250 μg, Ovitrelle, Serono, İstanbul, Türkiye). Oocytes were retrieved using trans vaginal ultrasound-guided double lumen needle aspiration after 34-35 h rec-hCG injection. Standard procedures were performed for the ICSI techniques, the follow-up fertilization and gamete-embryo development, and the embryo transfer. The luteal phase was supplemented by administering daily vaginal progesterone gel (Crinone 8%, Merck, Istanbul, Türkiye) and continued until menstruation or 8 weeks of gestation.

Patient characteristics were assigned as age, AMH level, 3rd day of FSH, E2 level, and AFC. The presence of concomitant adnexal pathology (i.e., Persistent ovarian cyst ≥4 cm, endometrioma, or tubal pathology) and the number of previous cycles were also evaluated. The cycles attempted in our clinic were evaluated. The history of previous cycles that were performed elsewhere was not included in the database.

Stimulation properties were defined based on controlled ovarian hyperstimulation (COH) protocols. Treatment protocols administered to patients were (1) flexible gonadotropin-releasing hormone (GnRH) antagonist protocol, (2) microdose flare-up protocol, (3) minimal stimulation protocols with clomiphene citrate (CC), and (4) GnRH agonist long protocol. Ovarian stimulation protocols, kind of used gonadotrophin, the total dosage of gonadotrophins, duration of ovarian stimulation (number of days) were recorded. E2 level, at 8th day and on hCG administration day were obtained from medical records. Cycle cancellation was defined as the presence of the ovarian hyperstimulation cycle discontinued before the egg retrieval step due to no follicle growing.

Cycle outcomes were defined as the follicle count of developing in different sizes at the 8th day of the cycle and on hCG administration day, the dominant follicle (≥14 mm) on hCG day. After oocyte retrieval, total oocyte and mature oocyte count, as well as empty follicle count, were obtained from cycle records. The oocyte maturity rate (MII oocyte number/total oocyte number), oocyte yield (total number of oocytes retrieved/AFC), and mature oocyte yield (number of mature oocytes retrieved/AFC) were calculated as previously defined and evaluated

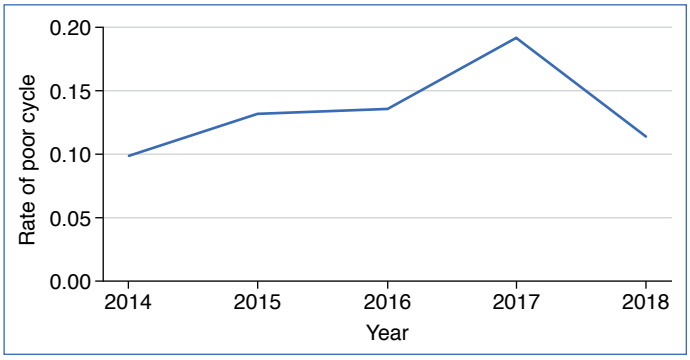

Figure 1: Trend of controlled ovarian cycle with poor ovarian response in the period between 2014 and 2018.

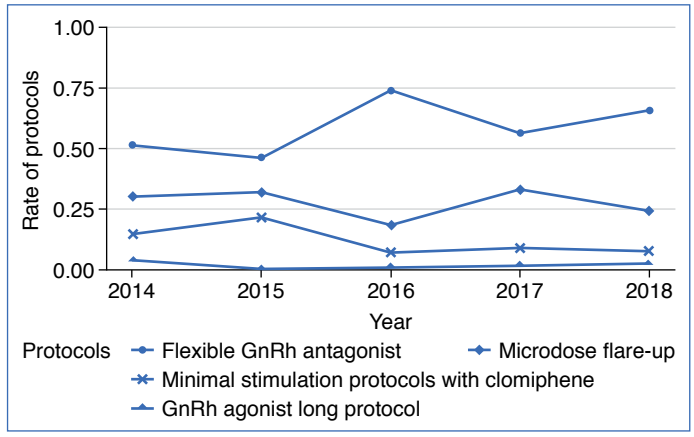

Figure 2: Changing trend in the used controlled ovarian stimulation protocols for cycles with poor ovarian response.

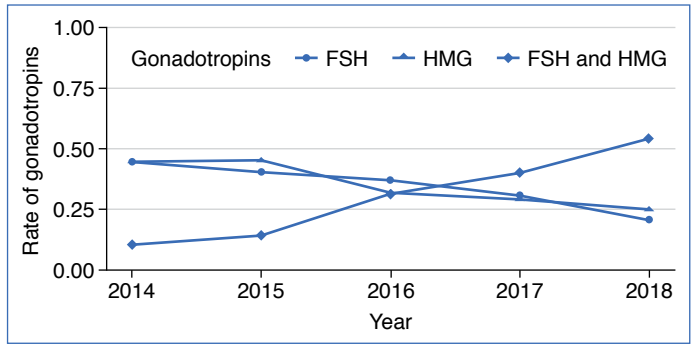

Figure 3: The kind of used gonadotropins to induce cycle over years.

trend of these outcomes in 5 years period.[18] The top-quality embryo was defined according to the ESHRE İstanbul consensus workshop on embryo assessment based on the observed morphology.[19] Following the ICSI procedure, the count of fertilized oocytes, top-quality embryos, and transferred embryos was recorded. Biochemical pregnancy was confirmed by a serial rise in serum human chorionic gonadotropin (hCG) concentrations 12 d after the embryo transfer.

Statistical Analysis

The numerical variables were presented as median (IQR), min-max values depending on their distributions. The distribution of the numerical variables was assessed using QQ, PP plots, skewness, kurtosis values, and Shapiro–Wilk's test. The numerical variables were compared among five groups using the Kruskal–Wallis test. The significant Kruskal–Wallis ANOVA test was followed by pairwise comparison using the Mann–Whitney U test where the Bonferroni adjusted p values ($p<0.05$ was statistically significant) were calculated. The results of the pairwise comparisons were given in the table with letters where groups with the same letter were not significantly different. Categorical variables were summarized by frequencies and percentages. The changes in the proportions of cycle number, presence of empty follicle, and cycle cancellation over 5 years were evaluated using the Cochran Armitage Trend test. The results were presented in the table. Over 5 years, the change estimates of the prevalence of poor cycle, the COH protocols (flexible GnRH antagonist protocol, microdose flare-up protocol, minimal stimulation protocols with CC and GnRH agonist long protocol), and the kind of used gonadotrophins (HMG, rFSH and the combination of gonadotropins) were evaluated with Cochrane-Armitage trend test and presented as figures. The statistical analyses were conducted using R 4.0 and $p<0.05$ was considered statistically significant.

RESULTS

Between 2014 and 2018 years, there were 776 cycles of 536 infertile women with POR that met the study criteria. We evaluated the changing trend of the prevalence of the cycle with POR at 5 year period. At first, we rejected the null hypothesis ($\chi^2(1)= 9.28$, $p=0.002$) that there is no linear trend in the proportion of poor cycles across the years. We calculated the changing trend using the Cochrane-Armitage trend test. We found that there appears to be a linear increase in the proportion of poor cycles in the 5 years ($p=0.002$). The result is given in Figure 1.

We also analyzed the change in the used COS protocols. We rejected the null hypothesis that there is no linear trend in the change of antagonist protocol and minimal stimulation protocols with clomiphene protocol across years ($\chi^2(1)=6.61$, $p=0.010$ and $\chi^2(1)=11.028$, $p<0.001$, respectively). There appears to be a linear increase in the change of the proportion of antagonist protocol, whereas there is a linear decrease in the proportion of minimal stimulation protocol with CC as years progress. The other two COS protocols did not show any significant changing trend over the years. The results are presented in Figure 2.

The trend analyses were calculated for the proportion of the different gonadotropin used. We reject the null hypothesis that there is no linear trend in the proportion of using alone rFSH, alone HMG, and the combination of rFSH and HMG across years ($\chi^2(1)=18.11$, $p<0.001$; $\chi^2(1)=18.62$, $p<0.001$; $\chi^2(1)=76.28$, $p<0.001$, respectively). There appears to be a linear increase in the proportion of the combination of gonadotrophins use, whereas there is a linear decrease in the proportion of only FSH or HMG usage as years progress (Fig. 3).

We reject the null hypothesis ($\chi^2(1)=4.26$, $p=0.039$) that there is no linear trend in the rate of cancelled cycle cross years. The sample estimate of the rate of the cancelled cycle in each year is given in Table 1. There appears to be a linear increase in the rate of a cancelled cycle as the years 'progress.

Table 1: Clinical characteristics and outcomes of controlled ovarian cycles with poor ovarian response over 5 years' period

	2014 (n=103)	2015 (n=153)	2016 (n=143)	2017 (n=257)	2018 (n=120)	p
Age (years) median (IQR)	35 (6)[a]	36 (4)[ab]	36 (5)[a]	37 (5)[a]	38 (4)[b]	*0.003[1]
Min–max	22–46	24–47	24–47	22; 48	25; 48	
Day-3 FSH (mIU/mL), median (IQR)	12 (4.9)[a]	11 (7.2)[a]	10.9 (5.9)[a]	9.5 (8.40)[b]	9 (6.9)[b]	*0.001[1]
Min–max	1.8–38	2.48–43	3.3–43	1.8–53	1.8–59	
Day-3 E2 (pg/mL) median (IQR)	38 (29)	41 (42)	42 (38)	45 (40)	40.5(35)	0.4047[1]
Min–max	10–336	7–365	7–405	6–537	6–260	
Day-3 AFC (n) median (IQR)	3 (3)[ab]	3 (2)[c]	4 (3)[ab]	4 (2)[a]	3 (2)[bc]	*0.001[1]
Min–max	1–9	1–9	1–8	1–8	1–8	
AMH (ng/mL) median (IQR)	0.13 (0.29)[ab]	0.08 (0.38)[a]	0.07 (0.38)[a]	0.2 (0.41)[b]	0.29 (0.48)[b]	*0.0011
Min–max	0.01–0.90	0.01–1.80	0.01–1.80	0–1	0.01–0.92	
Cycle properties						
Cycle number						0.098[2]
1st cycle, n (%)	55 (53.4)	85 (55.6)	91 (63.6)	172 (66.9)	68 (56.7)	
2nd cycle, n (%)	33 (32)	52 (34)	40 (28)	69 (26.8)	36 (30)	
3rd and above cycle, n (%)	15 (14.6)	16 (10.5)	12 (8.4)	16 (6.2)	16 (13.3)	
Total gonadotropin dose (IU) median (IQR)	3600 (1350)	3600 (1800)	3600 (1350)	3600 (1200)	3600 (1150)	0.994[1]
Min–max	1200–7200	900–9150	1800–9150	1500–7500	1800–6750	
Days of stimulation (day) median (IQR)	9 (4)	9 (3)	9 (4)	9 (3)	9 (2)	0.658[1]
Min–max	4–16	4–18	5–17	4–16	5–16	
E2 at 8th day (pg/mL) median (IQR)	158 (353)	87 (322)	192 (469)	144 (457)	207.5 (562.7)	0.086[1]
Min–max	0–995	0–1883	0–1734	0–1986	0–1006	
E2 on hCG day (pg/mL) median (IQR)	642 (484)	445 (425)	523 (474)	430(541)	477.5 (767.25)	0.129[1]
Min–max	0–1455	0–1883	0–1812	0–1447	0–1577	
Follicular development at 8th day (n) median(IQR) Min–max						
11–14 mm	0 (1)[ab]	0 (1)[a]	0 (2)[b]	0 (1.25)[ab]	0 (1.25)[ab]	*0.039[1]
	0–5	0–5	0–5	0–5	0–5	
15–16 mm	0 (0)	0 (0)	0 (0)	0 (1)	0(1)	0.130[1]
	0–3	0–4	0–3	0–4	0–4	
>17 mm	0 (0)	0 (0)	0 (0)	0 (0)	0 (1)	0.122[1]
	0–3	0–3	0–3	0–5	0–3	
Follicular development on hCG day (n) median (IQR) Min–max						
11–14 mm, (n)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0.817[1]

Table 1 (cont.): Clinical characteristics and outcomes of controlled ovarian cycles with poor ovarian response over 5 years' period

	2014 (n=103)	2015 (n=153)	2016 (n=143)	2017 (n=257)	2018 (n=120)	p
	0–3	0–5	0–4	0–5	0–4	
15–16 mm, (n)	1 (1)[ab]	0 (1)[a]	0 (1)[b]	0 (1)[ab]	0 (1)[ab]	*0.023[1]
	0–4	0–4	0–5	0–4	0–3	
>17 mm, (n)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	0.398[1]
	0–5	0–4	0–5	0–7	0–5	
Presence of cycle cancellation, n (%)	15 (14.6)	34 (22.2)	27 (18.9)	65 (25.3)	30 (25)	0.039[2]
Dominant follicle on hCG day (n) median (IQR)	2 (2)	2 (2)	2 (2)	2 (3)	2 (3)	0.208[1]
Min–max	0–7	0–8	0–5	0–12	0–9	
Total oocyte, (n) median (IQR)	2 (3)	1(2)	2(3)	1(2)	1(3)	0.051[1]
Min–max	0–7	0–9	0–10	0–9	0–8	
Mature oocyte, (n) median (IQR)	1 (3)	1 (2)	1 (2.5)	1 (2)	1 (2)	0.136[1]
Min–max	0–7	0–5	0–8	0–7	0–5	
Presence of empty follicle, n (%)	17 (14.4)	24 (20.3)	22 (18.6)	39 (33.1)	16 (13.6)	0.533[2]
Fertilized oocyte, (n) median (IQR)	1 (2)	0 (1)	0 (2)	0 (1)	0 (1)	0.284[1]
Min–max	0–5	0–5	0–6	0–5	0–4	
Oocyte maturity rate median (IQR)	1 (0.33)	1 (0.25)	0.9 (0.33)	1 (0.33)	1 (0.33)	0.110[1]
Min–max	0–2	0–1	0–1	0–1	0–1	
Oocyte yield median (IQR)	0.5 (0.75)	0.33 (0.75)	0.4 (0.75)	0.25 (0.6)	0.33 (0.75)	0.077[1]
Min–max	0–2.5	0–3	0–2.5	0–7	0–3	
Mature oocyte yield median (IQR)	0.33 (0.6)	0.33 (0.5)	0.25 (0.6)	0.2 (0.5)	0.25 (0.5)	0.137[1]
Min–max	0–2	0–2	0–2	0–6	0–3	
Embryo transfer day, (day) median (IQR)	2 (3)	0 (2)	0 (2)	0 (3)	0 (2)	0.363[1]
Min–max	0–4	0–4	0–4	0–5	0–5	
Transferred embryo (n) median (IQR)	1 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0.305[1]
Min–max	0–2	0–2	0–2	0–2	0–2	
Top quality transferred embryo, (n) median (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.207[1]
Min–max	0–2	0–2	0–2	0–2	0–2	
Pregnancy (n)	7	7	5	8	5	¶

Data are expressed as median with interquartile range or number with percentage as analyzed with Kruskal-Wallis ANOVA or chi-square tests as appropriate. 1: Kruskal-Wallis rank sum test; 2: Cochran Armitage Trend test; p values <0.05 are accepted as significant and presented as superscript letters. When the values are not different, they are marked with the same letter. E2: Estradiol; FSH: Follicle-stimulating hormone; AFC: Antral follicle count; AMH: Anti müllerian hormone; COS: Controlled ovarian stimulation; rFSH: Recombinant follicle stimulating hormone; HMG: Human menopausal gonadotropin; hCG: Human chorionic gonadotropin; n: Sample size; ¶: Data were not statistically analysed.

The parameters including the patient and cycle characteristics didn't show a linear trend. The mean age in 2014 was significantly lower than the mean in 2018. The cycles in the 2017 year had significantly higher AFC compared to ones in 2015 and 2018 ($p<0.001$ and $p=0.033$, respectively). The AMH levels in 2018 were significantly higher than both in 2015 and in 2016 ($p=0.007$ and $p=0.001$, respectively); levels in 2016 were lower than in 2017 ($p=0.014$). E2 level at 8th day and on the hCG administration day, gonadotrophin dose used, ovulation induction duration did not show any significant difference among the years.

There was no significant change in the trend of cycle outcomes during 5-year period. Among the cycle outcomes, the number of follicles in 11–14 mm size at 8th days in 2015 was higher than the ones in 2016 ($p=0.03$), and in the 2014 year, the follicle reached 15–16 mm size was higher compared with ones in 2017 ($p=0.02$). The other cycle outcomes including the presence of empty follicles, the oocyte data (the number of total oocytes and mature oocytes, the oocyte maturity rate, the oocyte yield, and the mature oocyte yield), the count of fertilized oocytes, and the embryo data (number of the top-quality embryo and transferred embryo count as well as transfer day) did not show significant change during 5 years period.

Concomitant adnexal pathologies were found totally as persistent ovarian cyst ≥4 cm (n=46), endometrioma (n=31), or tubal pathology (n=6).

DISCUSSION

In this study, we evaluated the changing trend of the prevalence of the ICSI cycle with POR in the large infertile women population over the 5 years. We also analyzed the change in the treatment protocols that preferred to cope with challenges in the poor response cycles during this period and in the kind and dosage of gonadotropins used. Furthermore, we evaluated alterations in the outcomes of the treatment cycle over this period. We obtained several data about changes in the management strategies used for infertile women with POR and their consequences. Our results have shown that there is an increasing trend in the prevalence of poor ovarian responder cycle with the highest rate being 19.16% in 2017. According to the latest data, most of the clinics revealed an increase in the incidence of PORs during the past 10 years. Data provided by the Society for Assisted Reproductive Technologies Clinic Online Reporting System indicated that the rate of diminished ovarian reserve (DOR) diagnosis increased from 19% in 2004 to 26% in 2011 and there was a 3.6% increase in the percentage of women older than 40 years of age at the cycle start.[11] Devine et al.[11] showed that there was an increase in the prevalence of DOR in patients who were <40 years old with 42% in 2011. In the USA, it was reported that 15% of patient underwent ART had DOR diagnosis in 2010, while in 2016 this rate raised to 31% and it reached to 32% in 2017.[20–22] These reports have revealed that the PORs population accounts for a substantial subset of women treated in IVF clinics nowadays.

Ageing is one of the several possible causes of diminished ovarian reserve. Naturally, the number of follicles tends to decrease as women's age increase and accelerates after 35 years of age.[23] From USA, ART, National Summary Reports showed that patients older than age 35 represented approximately 61% of all ART cycles performed in 2010 and approximately 62% of all ART cycles performed in 2016.[20,21] It also reported that the proportion of women aged above 39 years utilizing IVF and ICSI treatment gradually increased in European countries over the 15 years.[24] The results of the current study have shown that the age of poor responder women is in increasing trend with the highest median age of 38 years in 2018. Due to social or economic reasons, women have postponed their pregnancies. On the other hand, to easily accessible and affordable to ART cycles have encouraged infertile women of advanced age to attempt infertility clinics.[25] However, new technologies and treatment modalities have still been experimenting with and had debatable outcomes.[26,27] These new attempts have encouraged women of advanced age to demand infertility treatment. As a consequence, fertility clinics have encountered advanced-age women who are in the reproductive desire.

In this study, both median serum AMH levels and AFC were found a value lower than defined in the Bologna criteria.[2] Poor responder women population in 2016 had a lower AMH level compared with between 2017 and 2018. The highest median AFC was in 2017 and significantly higher compared with the value in 2015 and 2018 years. This fluctuation in AMH level and AFC did not show any significant trend among years and create any bias in terms of criteria included in the study. Nowadays, the basal (day 3) AFC and the serum AMH levels obtained at any time in the menstrual cycle are two valuable markers to predict POR to gonadotropins.[28] However, there are different results reported about which marker is the strongest predictor of ovarian response.[29,30] They have a similar predictive value for the poor response and have been used as a marker to predict ovarian reserve in the Bologna and POSEIDON criteria.[2,4]

The principle of COH is based on stimulation of the ovaries with gonadotrophin to achieve multiple follicles. Several treatment protocols have been proposed to obtain adequate follicle recruitment in PORs. These protocols may be grouped as pituitary down-regulation using GnRH agonists or antagonist protocols, and modified with different gonadotropins, CC, and adjuvant therapies such as the oral contraceptive pill, steroids, progestin's, L-arginine, and growth hormone.[31] The selection of treatment protocol has been performed based on the previous treatment outcomes. If no previous cycle has been performed, the choice is attempted according to clinics' experience or clinicians' preference taking into account patients' ovarian reserve, age, BMI. In this study, we found that the use of the antagonist protocol showed a linear increase trend, whereas the minimal stimulation protocol with CC had a decreasing trend. There was no change in the trend of using microdose flare-up protocols and GnRH long protocol. Several trials are comparing these protocols in terms of the total dose of gonadotropin, the number of oocytes obtained, and treatment outcomes. But there is no strong evidence to claim the use of any one of the particular interventions is superior to the others to improve the treatment outcomes in poor responders in IVF/ICSI cycles. Pooled data have demonstrated that in the GnRH antagonist group, the number of oocytes retrieved was significantly more and the total dose of gonadotropin hormones was significantly lower, compared with the conventional GnRH long protocol.[32,33] Data obtained from a worldwide survey showed that the GnRH antagonist protocol was the most popular treatment modality in PORs with 52% and followed by the short GnRH agonist flare-up with 20% and the microdose protocols with 15%.[7] In the current study, the

most popular protocol was the GnRH antagonist protocol with 58.5% over 5 years. It was followed by microdose flare-up protocol, minimal stimulation protocols with CC, and GnRH agonist long protocol with 28.3%, 11.6%, and 1.6% percentage, respectively. Treatment protocols with CC have been used as a patient-friendly regimen to reduce the number of gonadotropins and the burden of hormone injections. A systematic review reported that there was no conclusive evidence indicating that protocols with CC led to an increase in live birth or pregnancy rates, either in the general IVF population or in the poor responders.[34–37] A decreasing trend in CC regimens in this study may be a reflection of this report in our clinical management.

Our results demonstrated that in the cycles with POR, there was an upward trend in the combined use of gonadotropins from 10.7% in 2015 to 54.2% in 2018. The percentage of alone usage of gonadotrophins was found in decreasing trend for rFSH from 44.7% to 20.8% and for HMG from 44.7% to 25%. A Cochrane review has reported that there was no significant evidence of a difference between hMG and rFSH using in terms of ongoing pregnancy and/or live birth.[38] There is a tendency in the combined usage of gonadotropins. According to worldwide survey data, 42% of the responders reported that they were preferred to use HMG with rFSH. The percentage of alone rFSH or alone HMG usage was equal and reported as 20%.[7]

In this study, the cancelled cycle was defined as a cycle that was started with the intent to retrieve oocytes, but which was abolished before the oocyte retrieval. The percentage of cycles cancelled was in a significantly increasing trend. It reached 14.6% in 2015 to 25% in 2018. ART, National Summary Reports from the USA have reported that about 10% out of all cycles using fresh nondonor eggs or embryos were discontinued before the egg retrieval step in 2010, and cancelled cycle reached about 12% of all cycles in 2016.[20,21] In these reports, no or inadequate number of eggs obtained from ovarian stimulation have been reported as a cause of IVF cycle cancellation in an approximate range from 81% to 84%.[20,21] According to the Italian national ART register, 9.9% of performed IVF cycles were cancelled before oocyte retrieval in 2010; of which 6.7% of IVF cycles were cancelled for POR.[28]

There is no consensus about how long day ovarian stimulation should be continued before cycle cancellation. It was reported that 46% of cycles were stopped when treatment had no response after a minimum of 7–9 days; (31% after 4–6 days).[7] In this study, we found that the mean stimulation day to cancel the cycle for unresponsiveness to gonadotropins was 9 days inconsistent with previously reported.

In the period from 2015 to 2018, our results showed that there were no differences in the cycle outcomes including the number of retrieved total and mature oocytes, the oocyte maturity rate, the oocyte yield and the mature oocyte yield, the count of fertilized oocytes as well as the top-quality embryo and the number of the transferred embryo. Medical history, including ovarian or pelvic surgery due to endometriomas, ovarian cysts, tube or the other causes, and presence of persistent ovarian cysts greater than 40 mm diameter or endometriomas were also evaluated with trend analyses. However, these conditions are risk factors for POR.[2] We did not find an increasing trend about these risk factors, concomitant with the upward trend of the prevalence of the cycle with POR.

The major pitfall of the current study is no data about live birth outcomes. When we evaluated the medical records of cycles, we showed that βhCG results were recorded, but the ultrasound information about the fetal cardiac activity and live births were reported as verbal by patients and these data were recorded so. We thought that using verbal information might be creating a bias, so we decided not to include live birth outcomes in the analysis.

CONCLUSIONS

There is a clear increasing trend in the prevalence of cycle with POR over the 5 years. Aging is an obvious property of infertile women with POR. Our clinical management in the POR cycle has shown an alteration effort, consistency with the infertility specialists as in the other country. The changing trends of treatment protocol seem to be a tool for dealing with poor outcomes. On the other hand, this effort seems to have no better results. Treatment outcomes have been continuing to be a disappointment for clinicians and patients.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 05.06.2015, number: 90).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BD, HB; Design – NP, BD, NY; Supervision – BD, HB; Resource – BD, HB; Materials – BD, EA, NY; Data Collection and/or Processing – NP, BD, EA; Analysis and/or Interpretation – BD, EA, NY; Literature Search – NP, BD, NY; Writing – BD, NP; Critical Reviews – BD, NP.

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REFERENCES

1. Garcia JE, Jones GS, Acosta AA, Wright G Jr. Human menopausal gonadotropin/human chorionic gonadotropin follicular maturation for oocyte aspiration: Phase II, 1981. Fertil Steril 1983;39:174–9.
2. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L, et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: The Bologna criteria. Hum Reprod 2011;26:1616–24.
3. Boza A, Oguz SY, Misirlioglu S, Yakin K, Urman B. Utilization of the Bologna criteria: A promise unfulfilled? A review of published and unpublished/ongoing trials. Fertil Steril 2018;109:104–9.e2.
4. Poseidon Group (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number), Alviggi C, Andersen CY, Buehler K, Conforti A, De Placido G, et al. A new more detailed stratification of low responders to ovarian stimulation: From a poor ovarian response to a low prognosis concept. Fertil Steril 2016;105:1452–3.
5. Keay SD, Liversedge NH, Mathur RS, Jenkins JM. Assisted conception following poor ovarian response to gonadotrophin stimulation. Br J Obstet Gynaecol 1997;104:521–7.
6. Venetis CA, Kolibianakis EM, Tarlatzi TB, Tarlatzis BC. Evidence-based management of poor ovarian response. Ann N Y Acad Sci

2010;1205:199–206.

7. Patrizio P, Vaiarelli A, Levi Setti PE, Tobler KJ, Shoham G, Leong M, et al. How to define, diagnose and treat poor responders? Responses from a worldwide survey of IVF clinics. Reprod Biomed Online 2015;30:581–92.
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. Papathanasiou A, Searle BJ, King NM, Bhattacharya S. Trends in 'poor responder' research: Lessons learned from RCTs in assisted conception. Hum Reprod Update 2016;22:306–19.
10. Butts SF, Ratcliffe S, Dokras A, Seifer DB. Diagnosis and treatment of diminished ovarian reserve in assisted reproductive technology cycles of women up to age 40 years: The role of insurance mandates. Fertil Steril 2013;99:382–8.
11. Devine K, Mumford SL, Wu M, DeCherney AH, Hill MJ, Propst A. Diminished ovarian reserve in the United States assisted reproductive technology population: Diagnostic trends among 181,536 cycles from the society for assisted reproductive technology clinic outcomes reporting system. Fertil Steril 2015;104:612–9.e3.
12. Hu L, Bu Z, Guo Y, Su Y, Zhai J, Sun Y. Comparison of different ovarian hyperstimulation protocols efficacy in poor ovarian responders according to the Bologna criteria. Int J Clin Exp Med 2014;7:1128–34.
13. La Marca A, Grisendi V, Giulini S, Sighinolfi G, Tirelli A, Argento C, et al. Live birth rates in the different combinations of the Bologna criteria poor ovarian responders: A validation study. J Assist Reprod Genet 2015;32:931–7.
14. Kocourkova J, Burcin B, Kucera T. Demographic relevancy of increased use of assisted reproduction in European countries. Reprod Health 2014;11:37.
15. Centers for Disease Control and Prevention. National center for health statistics. Available at: https://www.cdc.gov/nchs/nsfg/key_statistics/i_2015-2017.htm#infertilityservices. Accessed Aug 24, 2021.
16. Niederberger C, Pellicer A, Cohen J, Gardner DK, Palermo GD, O'Neill CL, et al. Forty years of IVF. Fertil Steril 2018;110:185–324.e5.
17. Bozdağ H, Akdeniz E, Devranoğlu B, Haksever M, Bilgiç BE, Kutlu HT. Cytoplasmic abnormalities of mature oocytes have a significant effect on fertilization in Bologna poor responders. Turk J Med Sci 2018;48:750–8.
18. Cakmak H, Tran ND, Zamah AM, Cedars MI, Rosen MP. A novel "delayed start" protocol with gonadotropin-releasing hormone antagonist improves outcomes in poor responders. Fertil Steril 2014;101:1308–14.
19. Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: Proceedings of an expert meeting. Hum Reprod 2011;26:1270–83.
20. Centers for Disease Control and Prevention. Assisted reproductive technology national summary report 2010. Available at: https://www.cdc.gov/art/ART2010/PDFs/ART_2010_National_Summary_Report.pdf. Accessed Aug 24, 2021.
21. Centers for Disease Control and Prevention. Assisted reproductive technology national summary report 2016. Available at: https://www.cdc.gov/art/ART2016/PDFs/ART_2016_National_Summary_Report.pdf. Accessed Aug 24, 2021.
22. Centers for Disease Control and Prevention. Assisted reproductive technology national summary report 2017. Available at: https://www.cdc.gov/art/ART2017/PDFs/ART_2017_National_Summary_Report.pdf. Accessed Aug 24, 2021.
23. Broer SL, van Disseldorp J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P, et al. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: An individual patient data approach. Hum Reprod Update 2013;19:26–36.
24. Ferraretti AP, Nygren K, Andersen AN, de Mouzon J, Kupka M, Calhaz-Jorge C, et al. Trends over 15 years in ART in Europe: An analysis of 6 million cycles. Hum Reprod Open 2017;2017:hox012.
25. Ubaldi FM, Cimadomo D, Vaiarelli A, Fabozzi G, Venturella R, Maggiulli R, et al. Advanced maternal age in IVF: Still a challenge? The present and the future of its treatment. Front Endocrinol (Lausanne) 2019;10:94.
26. Osman E, Franasiak J, Scott R. Oocyte and embryo manipulation and epigenetics. Semin Reprod Med 2018;36:e1–e9.
27. Kawamura K, Ishizuka B, Hsueh AJW. Drug-free in-vitro activation of follicles for infertility treatment in poor ovarian response patients with decreased ovarian reserve. Reprod Biomed Online 2020;40:245–53.
28. La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: From theory to practice. Hum Reprod Update 2014;20:124–40.
29. Li R, Gong F, Zhu Y, Fang W, Yang J, Liu J, et al. Anti-Müllerian hormone for prediction of ovarian response in Chinese infertile women undergoing IVF/ICSI cycles: A prospective, multi-centre, observational study. Reprod Biomed Online 2016;33:506–12.
30. Nelson SM, Klein BM, Arce JC. Comparison of antimüllerian hormone levels and antral follicle count as predictor of ovarian response to controlled ovarian stimulation in good-prognosis patients at individual fertility clinics in two multicenter trials. Fertil Steril 2015;103:923–30.e1.
31. Keltz M, Sauerbrun-Cutler MT, Breborowicz A. Managing poor responders in IVF. Exp Rev Obstet Gynecol 2013;8:121–34.
32. Pandian Z, McTavish AR, Aucott L, Hamilton MP, Bhattacharya S. Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF). Cochrane Database Syst Rev 2010;CD004379.
33. Pu D, Wu J, Liu J. Comparisons of GnRH antagonist versus GnRH agonist protocol in poor ovarian responders undergoing IVF. Hum Reprod 2011;26:2742–9.
34. Kamath MS, Maheshwari A, Bhattacharya S, Lor KY, Gibreel A. Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation. Cochrane Database Syst Rev 2017;11:CD008528.
35. Selçuk S, Bostancı E, Küçükbaş M, Bilgiç BE, Kutlu HT, Devranoğlu B, et al. Comparison of outcomes of KOH/IUI and IVF treatment in advanced age infertile women. Zeynep Kamil Med J 2016;47:60–5.
36. Peker N, Turan G, Ege S, Bademkıran MH, Karaçor T, Erel Ö. The effect of clomiphene citrate on oxidative stress parameters in polycystic ovarian syndrome. J Obstet Gynaecol 2021;41:112–7.
37. Peker N, Ege S, Bademkiran MH, Aydin E, Karacor T, Obut M, et al. Can clomiphene citrate resistance be predicted by RDW-CV levels in infertile women with PCOS? Niger J Clin Pract 2019;22:1463–6.
38. Van Wely M, Westergaard LG, Bossuyt PM, Van der Veen F. Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. Cochrane Database Syst Rev 2003;CD003973.