

Stimulation techniques and protocols for poor responders in IVF cycles, future prospective methods and techniques, precaution programs.

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Abstract

Purpose: To identify trends regarding approaches, currently used by IVF centers in Greece, in order to treat poor responders.

Methods: A retrospective evaluation utilizing the results of a web-based survey was performed.

Results: Responses from 36 IVF centers via a web-based survey in Greece was conducted to elucidate optimal treatment strategies of poor responders. IVF specialized Doctors of units with a median of 300 IVF cycles per year were asked to anonymously fill in a set of questions on this complex topic. Results were analyzed, treatment strategies or combinations of protocols or adjuvant therapies used were compared. Also compared number of oocytes retrieved, as well as fertility and pregnancy rates among various IVF centers, based on their responses. A total of 36 centers participated in our survey, (from total 59 IVF centers) forming a web-based questionnaire. Due to responses on question if they observe an increase in the prevalence of poor responders ranging from: 1 - 3 % (8.6%, n=3), 4 - 9% (11.1%, n=4), mainly 20% (47.21%, n=17), but also greater than 20% (33.3%, n=12) in total of cases treated in Greek IVF centers. Also, the most common age group of poor responders is 40-50 years of age according to 80%(n=29) of respondents. **(Table 1)**. The review of international medical literature compared with answers received to our questionnaire suggests that no ideal treatment stimulation protocol exist. The following protocols have been described and compared: 1) Long protocol with Agonist (25.%, n=9) 2) Short protocol with Antagonist (52.8%, n=19) 3) Short protocol with Agonist (19.4%, n=7) 4) Stimulation only with Gonadotropins (5.6%, n=2) 5) Natural Cycle (66.7%, n=24) 6) Flare-up protocol (13.9%, n=5) 7) Duo-Stim Protocol (11.1%, n=4) 8) Delayed start protocol (11.%, n=4) 9) Protocol with cofollitropine (13.9%, n=5) 10) Clomiphene Citrate Protocol with or without Gonadotropins (41.7%, n=15) 11) Clomiphene Citrate Protocol with or without Aromatase inhibitors (19.4%, n=7) 12) Letrozole with or without recombinant FSH GnRH Antagonist Use (2.8%, n=1) 13) Letrozole with Clomiphene Citrate plus FSH & LH (2.8%, n=1) 14) Letrozole with FSH & LH plus GnRH antagonist (2.8%, n=1) 15) Protocol with Antagonists in combination with Letrozole (27.8%, n=10) . **(Table 2)**. We also represent results regarding the use of adjuvant treatment modalities to further improve results of stimulation cycles such as: a) Oestrogens (52.2%, n=12), b) Growth Hormone (4.3%, n=1), c) Testosterone (8.7%, n=2), d) Co-enzyme Q10 (56.5%, n=13), e) DHEA (78.3%, n=18). **(Table 3)**. All available therapeutic strategies used and according to international literature and in accordance with data derived from Greek IVF centers, oocyte harvesting ranges at low levels, around 2 to 4 oocytes (88.6%, n=3), 0-1 (8.6%, n=3), 5-8 (11.4%, n=4) and none of the IVF specialists collected more than 8 oocytes. Oocyte quality is also compromised, in (54.3%, n=19) only one oocyte of A quality was harvested, while 2 and 0, 3 or 4 oocytes of A quality were collected in (49.2%, n=15) and (5.7%, n=2). **(Table 4)** , according with data fully verifying the term poor responders. Moreover, we observed that abortion rates are increased >20% (41.2%, n=14), 10-20% (29.4%, n=10), 5-10% (11.8%, n=4) and 1-5% (17.6%, n=6) **(Table 5)**, as well as

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pregnancy rates are affected 5-10% (29.4%,n=10) and 10-20% (29.4%,n=10))(Table 6), while percentages of live pregnancies over 20% is observed in (17,6%,n=6) and under 6% in (23.5%,n=8)(Table 7).

Conclusion: All responses from the IVF specialists demonstrate the difficulty of treating this heterogenic group of subfebrile women. The egg donation is the treatment with increased success rate in comparison with different used treatments with agonists , antagonists cc, natural cycle, adjuvant treatments , the success rates of treatment in poor responders in IVF stimulation fluctuates from 7 to 24%. Prognosis is further improved if IVF specialist proposes and proceeds timely to the proper individualized therapeutic strategy.

Keywords: Subfertility; Poor responders; IVF protocols; Adjuvant therapies, IVF

1. Introduction

Fundamental significance to achieve pregnancy employing *In Vitro* Fertilization (IVF), is oocyte development and maturation. According to data, the number of oocytes retrieved presents as a predictor of the pregnancy outcome¹. A significant percentage of women undergoing oocyte stimulation in IVF, responds inadequately in the conventional protocols of ovarian stimulation with a significantly lower oocytes yield². Those women are categorized as “poor responders” they usually have reduced numbers of follicles, oocytes, high rates of cycle cancellations, low rates of egg fertilization, bad embryonic quality and as a result low rates of pregnancy and live births. The prevalence of POR ranges from 9 to 24% of women undergoing ovarian stimulation, while it seems to be rising -even up to 35% - due to changes in lifestyle and prioritizing regarding childbirth are constantly rising according to literature⁴. The limitation in quantifying the incidence of these patients among the infertile population is due to the lack of a consensus on the definition in literature. While there is more than one possible definitions, these patients tend to be of older maternal age, present with a history of poor ovarian response (POR) following conventional stimulation protocols, and/or have low ovarian reserve. In order to provide a predictive biomarker numerous tests had been proposed in literature⁵. The 2011 Bologna ESHRE working group on poor ovarian response has been the first real attempt to find a common definition^{6,7}. According to these criteria order to diagnose a patient with POR two of the three following criteria should be fulfilled: Maternal age over 40 years old, Anti-Mullerian Hormone (AMH) levels less than 1.1 ng/ml or Antral Follicle Count less than 5-7, and a previous poor response in a stimulated cycle (3 or less oocytes retrieved)^{6,7}. This special subgroup of IVF patients requires a personalized approach mainly due to the wide range of possible pathophysiological backgrounds entailed⁸ and there are no common characteristics that can be addressed through a holistic approach⁹. Current literature proposes numerous risk factors which could be the cause of a reduction in ovarian reserve, also including genetic factors¹⁰.

Treatment approaches for poor responders in order to achieve pregnancy utilizing IVF techniques, include numerous medical preparations, alone or in various combinations, the use of various therapeutic protocols suggested by international literature and with comparable results.¹¹⁻²⁰ It may be timely and essential to observe the prevalence of each protocol employed. the aim of this study is to demonstrate the therapeutic approaches used from specialized IVF centers in Greece, either in a university, public or private setting as well as the clinicians’ expectations regarding novel therapeutic approaches and protocols that may provide improved results.

2. Material and methods

A web based survey was conducted in Greece to elucidate optimal treatment strategies of poor responders. Clinicians employed in licensed IVF centers in Greece were asked to anonymously fill in a set of questions on this topic. A total of 36 -out of 59 licensed (61%)- centers participated in our survey, filling the web-based questionnaire. The questionnaire of 17 questions divided into 4 main sections. The first section was the preferred protocol employed for POR, the second section referred to administration of adjuvant therapies employed, the third referred to clinical observations and outcomes while the final section referred to possible future protocols and therapies for POR.

2.1. Statistical Analysis

Analysis of responses was based on the reported number of IVF cycles, median 300 of cycles per year who responded to the survey. For each question, the survey provided single answer multiple choice questions. The questionnaire was online for a total of 120 days from 12/2020to 03/2021. Data was collected from 36 IVF centers in Greece from a total of 59 licensed and accredited IVF centers (61%) and this sample size was considered sufficient.

3. Results

A total of 36 IVF centers from total 59 Greek IVF centers (61%) responded to the survey and met the computerized system's quality assurance standards. Regarding the first section on the preferred protocol employed, the most popular response was natural cycle IVF (24/36, 66.7% of responders), followed by the short agonist protocol (19/36, 52.8%) and clomiphene citrate with or without gonadotropins (15/36, 41.7%) (**Table 1**).

Regarding the adjuvant treatment administration, only 23 participants responded, the majority of whom opt to use Dehydroepiandrosterone (DHEA) (18/23, 78.3%), followed by co-enzyme Q10 (13/23 56.5%) and estrogens (12/23, 52.2%).

According to clinicians' observations the prevalence of POR in Greece is around 20% (17/36, 47.2%) or even higher (12/36, 33.3%), while the remaining clinicians observed a prevalence ranging between 4-9% (4/36, 11.1%) or less than 4% (3/36, 8.6%). The age of majority of POR patients is over 40 years old (28/36, 80%). Oocyte yield ranges at low levels, between 2 to 4 oocytes (29/36, 80.6%) in the majority of cycles, 0-1 (3/36, 8.6%), 5-8 (4/36, 11.4%) and none of the IVF specialists collected more than 8 oocytes. Oocyte quality is also compromised, with clinicians reporting that in the majority of cycles only one good quality oocyte was retrieved (19/36, 52.8%) followed by 2 (15/36, 41.7%) and other number of oocytes of good quality collected (2/36, 5.6%).[**Table 3**].

Using all available therapeutic strategies according to international literature and in accordance with data derived from Greek IVF centers, the clinicians report that they observed that pregnancy loss rates are increased >20% (41.2%, n=14), 10-20% (29.4%,n=10), 5-10% (11.8%,n=4) and 1-5% (17.6%,n=6). Further to this, the responders observed that live birth rates are affected with 5-10% (29.4%, n=10) and 10-20% (29.4%,n=10) being the most popular answers, while percentages of live birth over 20% is observed in (17.6%,n=6). On the other hand live-birth rates are lower than 5% are observed by almost a quarter of our responders (23.5%, n=8)[**Table 7**]. When evaluating possible novel treatments and approaches the majority of the responders opted for further treatment combinations (n=11, 42.3%), followed by administration of a molecular factor (n=6, 23.1%) and PRP (n=2, 7.1%)

4. Discussion

According to the results of this study, the majority of Greek IVF specialist use natural cycle IVF for POR patients. This may seem contradictory to international practices as according to the European Society for Human Reproduction and Embryology (ESHRE) guidelines the optimal protocol for POR patients is the mild stimulation protocol¹⁰. Nonetheless recent studies have proposed the natural cycle as an effective alternative to controlled ovarian stimulation, especially in advanced maternal age POR patients^{21,22}. Further studies and more specifically RCTs are required to evaluate the efficiency of the natural cycle IVF prior to concluding on its employment in poor responders as an effective alternative²³.

Regarding the administration of adjuvant therapies, the majority of our responders opted for DHEA, Co-enzyme Q10 (CoQ10) and estrogens, which is in part according to literature. Specifically, a recent meta-analysis reported that the former two, as well as growth hormone present with enhanced clinical outcomes when compared to no adjuvant treatment in poor responders²⁴. It should be noted that DHEA and CoQ10 may lead to higher clinical pregnancy rate, and CoQ10 is associated with lower cycle cancellation rate²².

As expected, the majority of the responders are over 40 years old and present with less than 3 oocytes retrieved. This is expected according to Bologna Criteria. However, it is possible that a POR patient may be either younger or yield a greater number of oocytes without being excluded according to Bologna Criteria. It may be imperative that this highly heterogenous population may have to be treated differently, especially in the era of personalized medicine. It may be time to evaluate the profile of each patient and propose a more individualized approach that may be the key in this time-sensitive group of patients. As noted both in the results of our study and in current literature, POR patients have a lower clinical pregnancy and live-birth rate, when compared to normal responders²⁵. The analysis of the results rises the question whether we could improve some or even all of the above compromised parameters utilizing new pharmaceutical and supplementary therapeutic strategies. Ovarian rejuvenation using PRP is a new experimental approach which helps natural production of oocytes in ovaries. It is a remarkable alternative to oocyte donation. Furthermore, it creates expectations in women of advanced reproductive age who have decreased numbers and quality of oocytes. Literature studies shows that PRP injections into the ovaries are safe, beneficial, and a natural treatment that may help women with premature ovarian insufficiency to give birth to their own child²⁶. However, large RCTs are required prior to cementing PRP's safety and efficacy. Optimization of oocyte quality, individualized treatment two more propositions from responders.

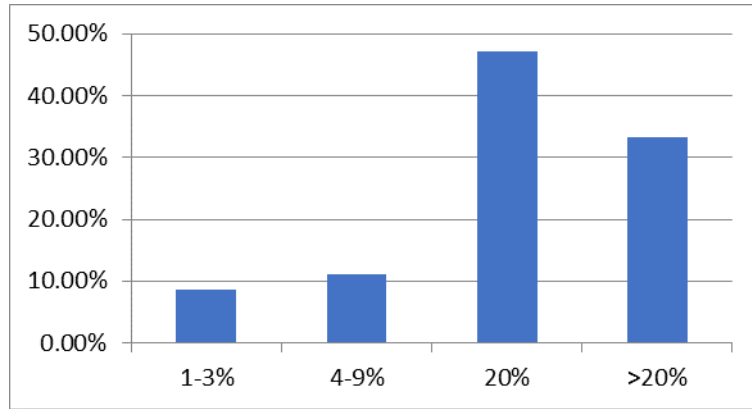


Table 1 Increased Amount of Poor Responders (number of responders)

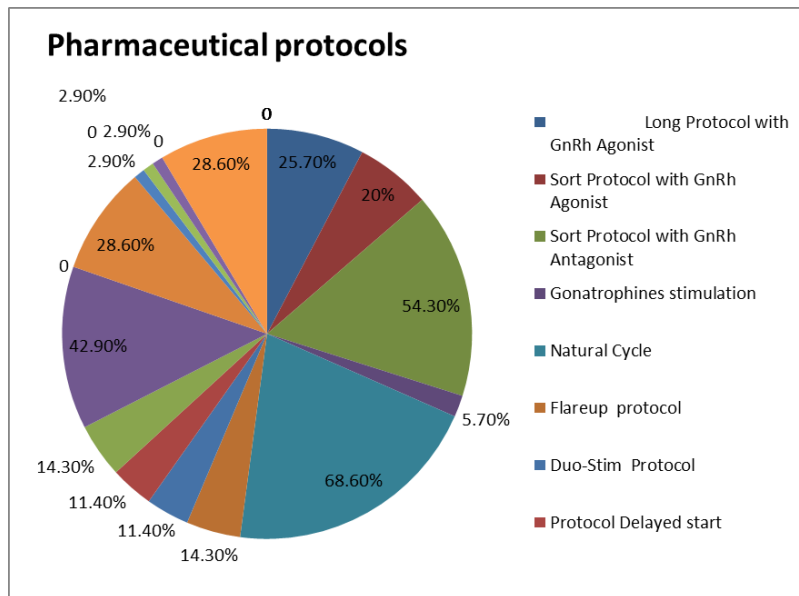


Table 2 Different Pharmaceutical protocols to treat Poor Responders.

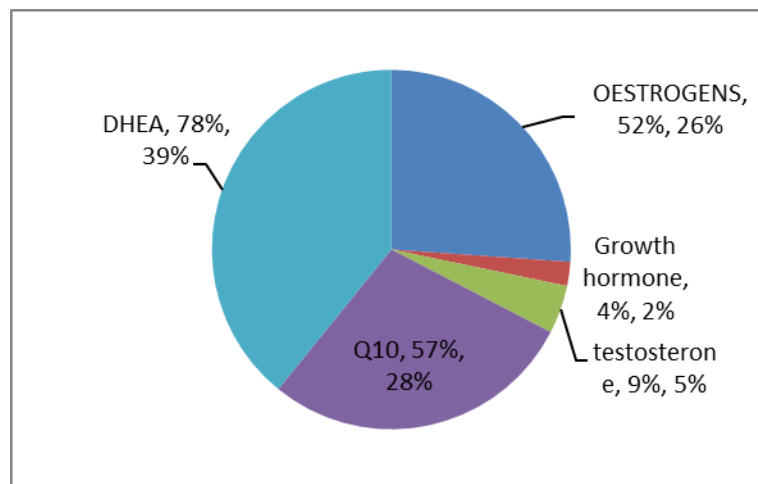


Table 3 Adjuvant treatment modalities used to improve results of stimulation cycles

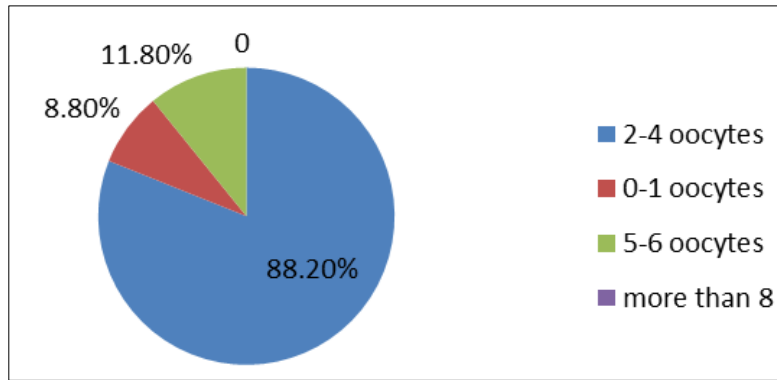


Table 4 Oocyte retrieval rates .With all available therapeutic strategies according to international literature and in accordance with data derived from Greek IVF centers, oocyte harvesting ranges at low levels

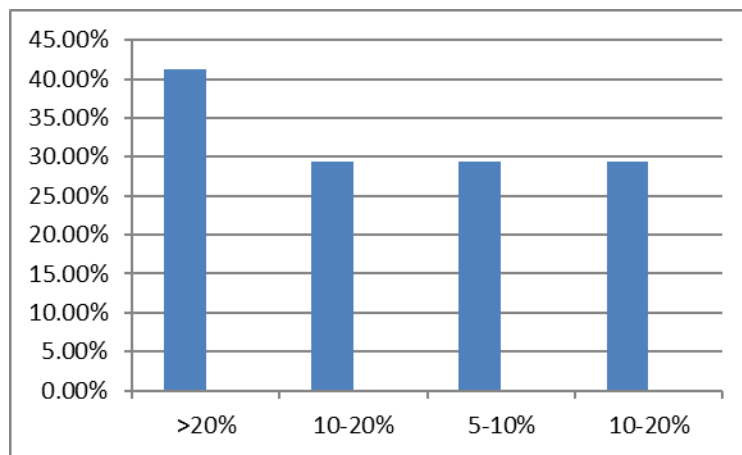


Table 5 Miscarriage rates live birth rates are affected.

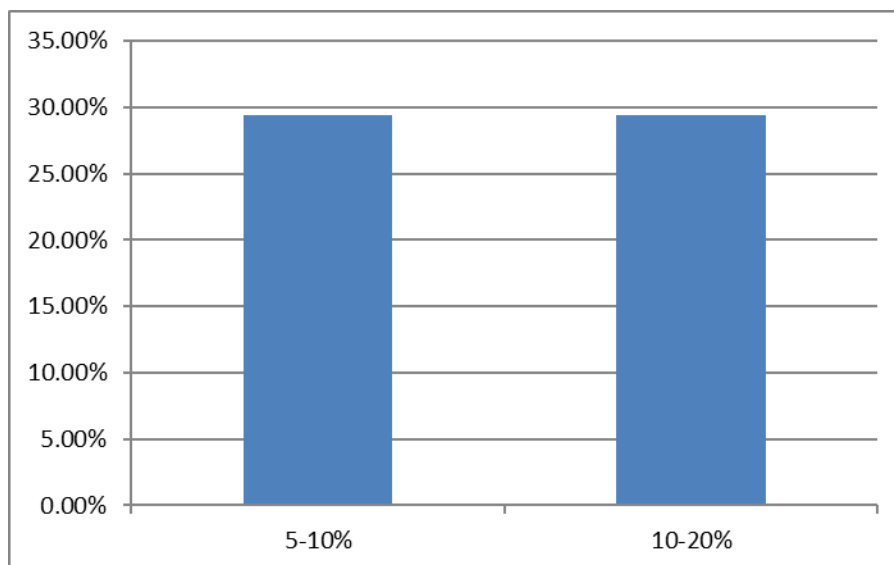


Table 6 Live pregnancy rates are also affected.

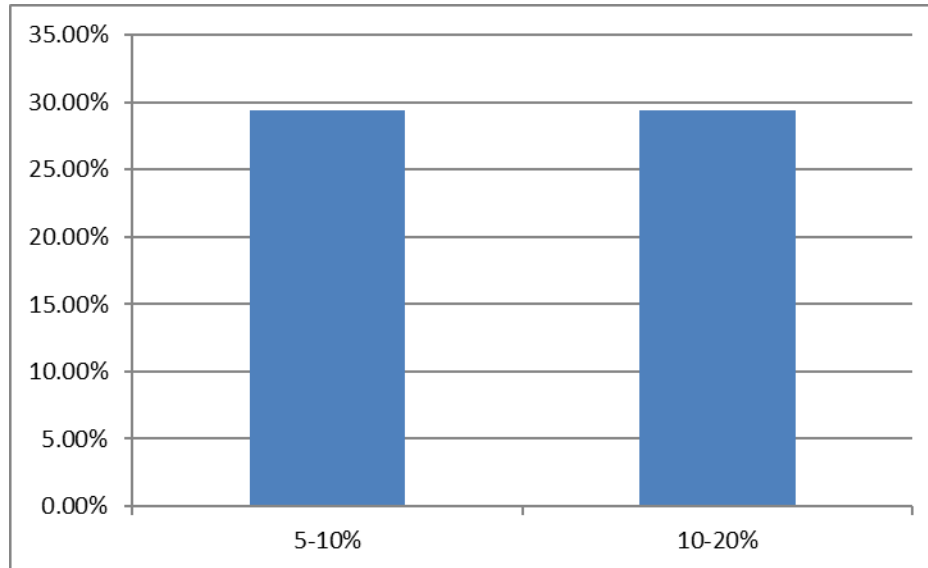


Table 7 Index of live pregnancies

5. Conclusion

In conclusion, the best available evidence supports that the treatment of the expected poor ovarian response patient should be individualized in all steps of ART, including the choice of GnRH analogue, the gonadotropin type and dose, ovulation trigger, and the possible use of adjuvant therapies. However, essentially the option with the higher pregnancy success rates is ovarian donation. It is a medically simple technique, but an emotionally and psychologically complicated process for the couple who chooses this option. Previous and up to time international studies according with our results to treat “poor responders”.

How can we help poor responders earlier, cost-effectively and by the time using new therapeutic approaches, or consultations with IVF specialized doctors possibly between 30 to 35 years of age? Maybe a universal educational program targeting at women of childbearing age at the age of 30 to 35, utilizing consultation by specialists in human reproduction would help profoundly, providing women with information regarding available options for their family planning. A consultation with experts could save financial resources in pharmaceutical and nursing expenses, as well as possible future side effects resulting from multiple IVF cycles and due to medical complications of IVF pregnancies such as diabetes mellitus, preeclampsia, placental abruption, premature rupture of membranes etc.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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