Modern therapeuthic option for enhancing oocyte yield for assisted reproductive technology in poor responders

Opțiune terapeutică modernă pentru creșterea numărului de ovocite în programele de reproducere asistată la „poor responders"

Irina Pacu[1,2], Iulia Tarcomnicu[1], C. Ionescu[1,2]

1. "Carol Davila" UMPh, 2. Obstetrics and Gynecology Clinic, "Sf. Pantelimon" Emergency Hospital Bucharest

Abstract

Introduction. *Management of poor responders in IVF is quite a challenge as the incidence of poor ovarian responders among infertile women is increasing and despite the hudge number of papers about this topic there are insufficient evidence to recommend the best approach for these cases.* ***Matherial and Methods.*** *The aim of the study is to evaluate the number of oocyte and pregnancy rates for poor responders using classic antagonist protocols versus the Duplex protocol that features a dual stimulation, with the second stimulation started immediately after the first oocyte retrieval. This modern approach can be succesfull used due to large availability of oocyte and embryo vitrification offering access to an emerging new realm of "no-loss cryopreservation" and bringing new options in assisted reproductive technologies. Our study compare two groups of patients, both with poor response to ovarian stimulation for IVF, according to Bologna criteria. For the first group we have used antagonist protocol using 300-450UI FSH per day, Cetrorelix 0.25mg per day starting on ovarian stimulation day 6 and GnRH of HCG trigger; for the second group with Duplex protocol we have used a similar protocol for the first stimulation and after the oocyte retrieval we started the second similar stimulation in the day of first oocyte retrieval. In the second group we have made embrio vitrification in all cases.* ***Results.*** *The first and second stimulation in the second group provided similar number of oocytes and embrios, so Duplex protocol doubled the final blastocysts yield. Pregnancy rate is better in second group.* ***Conclusions.*** *Our dates are similar to those from similar literature findings but we consider these only preliminary data because of a small number of cases. The protocol was well tolerated in all cases. Duplex protocol is a modern and no risk option not only for poor responders but for cases that need a short time for fertility preservation.*

Keywords: *poor responders, Duplex protocol, fertility preservation*

Rezumat

Introducere. *Managementul pacientelor „poor responder" este o provocare în fertilizarea in vitro din cauza incidenței crescute a acestora și deși a fost publicat un număr mare de articole care abordează această temă, ele nu oferă o metodă clară de abordare a acestor cazuri.* ***Material și metode.*** *Scopul acestui studiu este de a evalua numărul de ovocite și rata de sarcini obținute comparând protocoalele clasice pentru poor responders cu protocolul Duplex care are la bază două stimulări cu cea de-a doua stimulare începută imediat după recoltarea primelor ovocite, in faza lutеală. Această abordare modernă poate fi folosită în siguranță si cu succes datorită disponibilității vitrificării embrionare ceea ce deschide un nou domeniu de „crioprezervare fără pierderi" conducând astfel către noi opțiuni în tehnicile de reproducere asistată. În studiul nostru comparăm cele două grupuri de pacienți, ambele cu răspuns nesatisfăcător la stimulare ovariană pentru fertilizare in vitro (FIV), conform criteriilor Bologna. Pentru primul grup am folosit protocolul cu 300-450 UI FSH pe zi, antagonist de GnRH (Cetrorelix 0,25 mg pe zi din ziua 6 de stimulare) și triggerul ovulatiei cu HCG. Pentru cel de-al doilea grup cu protolul Duplex am realizat prima stimulare în mod similar cu cea din primul grup iar după prelevarea ovocitelor am reluat același protocol de stimulare. La cel de-al doilea grup am făcut verificarea embrionilor in toate cazurile, cu vitrificare corespunzatoare. Embriotransferul s-a realizat cu embrioni crioprezervati.* ***Rezultate.*** *Prima și cea de-a doua stimulare din grupul al doilea de paciente au furnizat un număr similar de ovocite și embrioni, astfel prin protocolul Duplex s-a dublat numărul total de blastociști și astfel randamentul. Rata sarcinilor este mai bună în cel de-al doilea grup.* ***Concluzii****. Datele obținute sunt similare cu cele ale altor publicații dar le considerăm preliminare din cauza numărului redus de cazuri. Protocolul a fost tolerat bine la toate pacientele. Protocolul Duplex este o opțiune modernă ce nu asociază riscuri fiind utilă nu numai la pacientele „poor responder" dar și la pacientele la care este necesara prezervarea fertilității înainte de tratamentul oncologic, factorul timp fiind decisiv.*

Cuvinte-cheie: *poor responder, protocolul Duplex, prezervarea fertilității*

1. Introduction

The field of assisted reproduction is a modern area with needs for great steps forward to be made in terms of clinical knowledge and technological development. As women progress through their reproductive years, they experience a decline in fertility and fecundity and assisted reproductive techniques (ART) is the solution for most cases. One of the most fundamental steps to achive good results is still related to the number of eggs obtained after hormonal stimulation.

As the "infertility age" became elder, the number of oocyte retrieved is smaller and we can find a great and important category of "poor responders", a group of pa-

tients increasing with each study. The limited number of oocytes and eggs remains the main problem in optimizing pregnancy rate[1,2].

2. Poor responders. Bologna criteria

The concept of poor ovarian response was introduced 30 years ago but there was no consensus about a common definition until ESHRE consensus in 2011, in Bologna. There were a huge variety of definition for poor ovarian response: number of mature follicles on the day of human chorionic gonadothrope hormone (HCG) administration (<2 to<5)[3], number of oocyte retrived (<3 to <6), the serum estradiol level (300 to <600pg/ml on the day of HCG) or the total and/or daily dose of gonadotropin used[2,4]. A survey (IVF-Worldwide, 2010) conducted in 196 centers from 45 countries shows a huge variety in defining and treating poor ovarian responders (POR) and suggest a great need for a consensus. The ESHRE workshop in Bologna reached an agreement on the following issues:

a. The risk factors are maternal age over 40 and all the genetic or acquired conditions linked to a reduced amount of resting follicles.

b. A POR is represented by a cycle canceled (less than 3 follicles) or the collection of less than 4 oocytes in response to ovarian stimulation protocol with minimum 150 UI of FSH daily. Oocyte maturity is not included in this criteria.

c. Any marker can help the prediction of POR. The number of antral follicles and AMH seem to have the best sensitivity and specificity.

d. Each criterion (risk factor, previous cycle and ORT) used alone is insufficiently accurate to identify women with the highest probability of being a real POR[5].

Bologna consensus shows that at least two of the following features must be present for including a case in POR:

1. advanced maternal age over 40 years old or any risk factor for POR

2. a previous POR: <4 oocytes with a conventional stimulation protocol

3. an abnormal ovarian reserve test (number of antral follicles under 5-7 or AMH<0.5-1.1 ng/ml)[2,5].

Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT.

This definition is the first realistic attempt by a scientific community to standardize the definition of POR in a simple and reproductible manner. The aim is to identify the cases with poor response, to include all these cases in this category in order to use special protocols for ovarian stimulation for these cases and not to exclude poor prognosis patients from IVF programmes.

3. Protocols for POR

Although many protocols with different doses and types of gonadotropines have been proposed in the literature for the managenet for poor responders, there is no ideal protocol to solve the problem and the question still exists. Ovarian stimulation was designed to improve reproductive technologies outcome by providing more than one ovocite to inseminate[2].

In normoresponders in the last twenty years, the protocol of choice was the combination of gonadotropines and gonadotropin-releasing hormone (GnRH) agonist. In poor responders it may induce an excessive ovarian suppression that could lead to a reduced or absent follicular response. For these patients we had some options:

(i) To initiate the suppression with GnRHa in the luteal phase and then to stop or lower it.

(ii) To decrease the length of suppression by descreasing the duration of GnRHa using short, mini or microdose flareup protpcols.

(iii) To use GnRHantagonists to prevent premature LH raise. Probably, now this is the mostly used regimen as its improvement for patients compliance, decreased number of days and dose of gonadotropines and reduced risk for ovarian hiperstimulation syndrome. For POR the advantage is that agonists are not used in the first days of stimulation (the stage of follicular recruitment) and the suppression of GnRH is not present at this moment, obtaining a more natural follicular recruitment without great inhibitory effect[4,6].

(iv) Alternative approaches like: addition of estradiol in luteal phase, addition of recombinant LH, addition of growth hormone (GH) with probably better results (there are no studies to suggest routinary addition of GH in poor responders) but more expensive, addition of androgens, addition of aspirin, natural cycles of IVF, oocyte cryopreservation[7,8,9].

But despite the huge number of studies about the optimum regimen for poor responders, at the moment systematic reviews suggest that insufficient evidence exists to recommend most of the treatment proposed to improve pregnancy rate in this group; this subject remains one of the most challenging tasks in reproductive medicine[2].

Duplex protocol. Our experience

The ovarian stimulation protocols used in ART aim to modify the hormonal environment of the follicular phase to fool the natural mechanism of single follicular dominance that is normal. This was the beginning of the idea that we can use protocols that prevent the decrease in FSH level in the mid follicular phase, which is responsible for single follicular dominance. In the last years the new tehniques of oocyte or embryocryopreservation go to a new concept that ovarian stimulation can be tottaly disconnected from the cycling phases of endogenous gonadotropins without any detrimental consequences if no fresh embryotransfer (ET) takes place[10]. This is why Kuang et al. (2014) capitalized on the combined achivment of the random-star protocols and embryo vitrification by testing the possibility of deliberatelty starting ovarian stimulation during the luteal phase. The investigators showed that luteal phase start stimulation is feasible and produced a normal number of competent oocytes and optimal pregnancy rates from cyopreserved ET cycles.

Kuang et al. (2014) reported a trial of 242 participants; ovarian stimulation was accomplishing using a combination of aromatase inhibitors (letrozole 2.5 mg/day) and HMG 9225UI/day) starting after spontaneous ovulation until three or more follicles had reached a diameter of 188mm or bigger. Final oocyte maturation was triggered using triptoreline 0.1mg and all 242 patients underwent oocyte retrieval

Table 1 The patients that received a dual stimulation protocol, who fulfilled Bologna criteria for poor responders, based on prior ovarian stimulation outcome, baseline hormonal levels and age

	Age	AMH ng/ml	AFC	No. of previous canceled cicles	Med. no. of oocytes/ previous cycles	No. of oocytes first stim.	No. of oocyte second stim	Pregnancy
1	40	0.90	7	0	4	4	3	+
2	40	0.87	7	1	3	3	3	+
3	40	0.77	6	0	4	3	2	-
4	41	0.80	5	2	0	2	3	-
5	41	0.95	7	1	3	3	4	+
6	41	0.71	6	1	0	3	2	-
7	42	0.66	4	1	3	3	3	-
8	42	0.80	7	0	3	3	4	+
9	43	0.71	5	1	0	3	2	-
10	43	0.55	6	2	0	3	4	-
11	44	0.82	5	2	0	2	2	-

which yielde 13.1 oocytes on average and clinical pregnancy rate in cryoET at 48.9%. The same investigators reported a study including 38 patients who fulfilled the Bologna criteria for poor responders. For the first stimulation they used a combination of clomiphene citrate 25 mg per day from day 3, letrozol 2.5 mg/day from day 3 for 4 days and FSH 150UI/ day from day 6, without GnRH antagonist. The second stimulation was started after the first oocyte retrieval with 2.5 mg letrozol/day and 225UI FSH/day. Ovulation induction was with triptorelin 0.1 mg. Premature ovulation was prevented using ibuprofen 600 mg/day on the day of triggering ovulation and the day after. Only 30 from 38 patients underwent two consecutive retrievals, with second ovarian stimulation yielding a larger number of oocytes and embryos than the first[10,11,12]. We want to present data preliminary data from our patiens that we offered a dual stimulation protocol. We had 11 patients (octomber 2014 - march 2015) who fulfilled Bologna criteria for poor responders, based on prior ovarian stimulation outcome, baseline hormonal levels and age. In our Duplex protocol both first and second stimulation used a similar regimen: a dose of 225-300UI FSH per day, cetrorelix 0.25 mg per day starting on ovarian stimulation day 6 and final oocyte maturation using 10000UI HCG. In all cases we made embryo vitrification and cryoET. The number of oocytes were similar in first and second stimulation and the final number of oocytes and embryos doubled. The dose of FSH for second stimulation was similar with the first one. Data from our patients were similar to Kuang's report (published in the issue of Reproductive Medicine online, 2014a) and Rebecca Mofat (Reproductive Biomedicine Online, 2014, 29,659-661). We found a good general tolerance of the second stimulation without any side effects. The results are shown in Table 1.

Conclusions

Even if we had a small number of cases in our study, our findings indicate that Duplex protocol can be a correct option for poor responders. The common use of vitrification and a good rate of success for cryoET can make this protocol a common one for poor responders. It has no side effects and can be the best option for patients who need fertility preservation and time can be very important for them, as we retrieve by this way a greater number of oocytes in a short period of time, less than 30 days. ■

References

1. Polyzos, N. P. and Devroey, P.- A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the tunnel ?- Fertility and Sterility, vol.96, no.5, pp 1058. e7-1061.e7, 2011.
2. Ubaldi, F., Vaiarelli, A., D'Anna, R., Rienzi, L.- Review article-Management of poor Responders in IVF: Is there anything new?, Hindawi Publishing Corporation BioMed Research International, Vol. 2014, pp.1-6.
3. Lashen, L., Ladger, W., Lopez-Bernal, A., and Barlow, D.- Poor responders to ovulation induction: is proceeding to in-vitro fertilization worthwhile?, Human Reproduction, vol. 14, no.4, pp. 964-969,1999.
4. Schoolcraft, W, Schlenker, T., Gee, M., Stevens, J., and Wagley, I.-Improvent controlled ovarian hyperstimulation in poor responder in vitro fertilization patients with a microdose follicle stimulating hormone flare, growth hormone protocol, Fertility and Sterility, vol. 67, no.1, pp 93-97, 1997.
5. Ferraretti, A.P., La Marca, A., Fauser, B.C.J.M., Tarlatzis, B., Nargund, G., Gianaroli, L.on behalf of the ESHRE working group on Poor Ovarian Response Definition - ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria, Human Reproduction Advance Access published April 19, 2011, Vol.0, No.0, pp. 1-9.
6. Hughes, E. G., Fedorkow, D. M., Daya, S., Sagle, M.A., Vand de Kopel, P., and Collins, J., A.- The rutine use of gonadotropin releasind hormone agonists prior to in vitro fertilization and gamete intrafallopian transfer: a meta-analysis of randomized controlled trials, Fertility and Sterility, vol. 58, no.5, pp. 888-896, 1992.
7. Reynolds, K., A., Omurtag, K. R., Jimenez, P.T., Rhee, J.S., Tuuli, M., G., and Jungheim, E.S.- Cycle cancellation and pregnancy after luteal estradiol primiting in women defined as poor responders: a systematic review and meta-analysis, Human Reproduction, vol 28, no. 11, pp. 2981-2989, 2013.
8. Fanchin, R., Salomon, L., Castelo-Branco, A., Olivennes, F., Frydman, N., and Frydman, R. - Luteal estradiol prea-treatment coordinates follicular growth during controlled ovarian hyperstimulation with GnRh antagonists, Human Reproduction, vol. 18, no. 12, pp. 2698-2703, 2003.
9. Hill, M. J., Levens, D.E., Levy, G., et al. -The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis, Fertility and Sterility, vol. 97, no. 5, pp. 1108. El-1114. E1, 2012.
10. Moffat,R., Pirtea, P., Gayet ,V., Philippe Wolf, L., Chapron, C., Dominique de Ziegler- Dual ovarian stimulation is a new viable option for enhancing the oocyte yield when the time for assisted reproductive technnology is limited, Reproductive BioMed Online (2014) 29, pp. 659-661.
11. Kuang, Y., Chen, Q., Hong, Q., Lyu, O., Shoham, A. Ai, Y, Fu, Z. - Double stimulation during the follicular and luteal phases of poor responders in IVF/ ICSI programmers (Shaghai protocol), Reprod BioMed Online 29, 2014 b.
12. Cakmak, H., Katz, A., Cedars, K. I., Rosen, M.P.,. Effective method for emergency fertility preservation: random-start controlled for emergency fertility prezervatin: random-start controlled ovarian stimulation. Fertil. Steril 100, 1673-1680, 2013