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Type and dose of gonadotropins in poor ovarian responders: does it matter?

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Liese Boudry, Annalisa Racca, Herman Tournaye and Christophe Blockeel

***Abstract*:** Infertile patients with a diminished ovarian reserve, also referred to as poor ovarian responders, constitute a substantial and increasing population of patients undergoing *in vitro* fertilization. The management of patients with poor ovarian response is still a controversial issue. Almost a century has passed since the introduction of the first gonadotropin. A broad collection of urinary and recombinant gonadotropins, including biosimilars, is commercially available now. Despite great advances in assisted reproductive technology, there remains uncertainty about the optimal treatment regimen for ovarian stimulation in poor ovarian responders. Although oocyte donation is the most successful and ultimate remedy for poor ovarian responders, most patients persist on using their own oocytes in several attempts, to achieve the desired pregnancy. The aim of this review is twofold: first, to provide an overview of the commercially available gonadotropins and summarize the available evidence supporting the use of one or another for ovarian stimulation in poor ovarian responders, and second, to address the controversies on the dosage of gonadotropins for this specific *in vitro* fertilization population.

Keywords: gonadotropin dose, gonadotropins, ovarian stimulation, poor ovarian responder

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Correspondence to:
Liese Boudry
Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, 1090, Brussels, Belgium
Liese.Boudry@uzbrussel.be

Annalisa Racca
Department of Obstetrics, Gynecology and Reproduction, Hospital Universitari Dexeus, Barcelona, Spain

Herman Tournaye
Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium; Department of Obstetrics, Gynecology, Perinatology and Reproduction, Institute of Professional Education, Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation, Moscow, Russia

Christophe Blockeel
Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium; Department of Obstetrics and Gynaecology, University of Zagreb, Zagreb, Croatia

Introduction

The introduction of ovarian stimulation (OS) improved outcomes in *in vitro* fertilization (IVF) significantly through the administration of exogeneous gonadotropins, the key regulators of ovarian follicular development. Although the aim of OS is to induce the growth and maturation of multiple follicles in order to collect an adequate number of oocytes for IVF or intracytoplasmic sperm injection (ICSI), in about 9–24% of the patients a poor response is encountered, depending on the definition used.[1] In those patients, the question rises whether it is meaningful to change the type or dose of gonadotropins in order to increase the oocyte yield and improve prognosis.

Poor response

Definition

To evaluate the effect of a specific intervention, consensus on the definition of poor response is crucial. Formerly, in the literature, this definition was author-defined and very divergent.[2] This lack of uniformity led to the development of the Bologna criteria (BC), established by a working group of the European Society of Human Reproduction and Embryology (ESRHE) in 2011.[3] However, as the BC still contained various poor ovarian responder (POR) subpopulations with diverse baseline characteristics and different clinical prognoses, the usefulness of these criteria in clinical and scientific practice was questioned.[4]

In 2016, in an attempt to further reduce the heterogeneity, the POSEIDON (Patient Oriented Strategies Encompassing IndividualizeD Oocyte Number) classification was developed, dividing the PORs into four subgroups, defining them as 'low prognosis patients' rather than 'poor responders'.[5] Subdivision is based on age, prestimulation ovarian reserve tests (ORTs) and previous cycle performances. In practical terms, this allows the distinction of two main categories,

namely, the 'expected' PORs (groups 3 and 4) and the 'unexpected' PORs (groups 1 and 2). The latter have normal prestimulation characteristics, but react suboptimally to normal/conventional OS and are also called 'hypo-responders'. The purpose of the POSEIDON criteria is to guide personalized treatment protocols for second and subsequent cycles. Given the lack of validation, the Poseidon criteria are not yet generally adopted in clinical practice. However, data on reproductive outcomes for the different subgroups are growing[6,7] and the first clinical trials using the POSEIDON criteria in their design are being published.[8]

Aim of treatment

Patients fitting the POSEIDON criteria have a low prognosis in assisted reproductive technology (ART) based on a reduced number of retrieved oocytes and consequently fewer available embryos for transfer. The number of oocytes has shown to strongly influence the cumulative live birth rate (CLBR) and therefore IVF success rates across all female age groups.[9] In Bologna poor responders, accordingly, each additional oocyte enhances live birth rate (LBR).[10] Therefore, if one gonadotropin is superior to another in the ability to generate an adequate follicular response, particularly in (unexpected) poor responder patients, it could make an important difference. However, based on the age of the patient and the associated increase in embryo aneuploidy,[11,12] the number of oocytes needed to maximize live birth should be individualized.[13,14]

Gonadotropins—type

The three gonadotropins, follicle stimulating hormone (FSH), luteinizing hormone (LH), and human chorionic gonadotropin (hCG), are members of the glycoprotein family, which also includes thyroid-stimulating hormone (TSH).[15] These glycoprotein hormones are heterodimers consisting of noncovalently associated alpha and beta subunits. The alpha subunit contains 92 amino acids (AA) and is identical in FSH, LH, and hCG (and TSH). On the contrary, the beta subunits are unique and confer biological specificity.[16] The beta subunit of FSH is composed of 111 AAs, whereas the one of LH contains 121 AAs, identical to the beta subunit of hCG, which additionally contains another 23 AAs. Both hCG and LH act on the same receptor [luteinizing hormone/choriogonadotropin receptor (LHCGR)], but they do not elicit the exact same cellular and molecular response.[17]

Gonadotropins are currently the cornerstone in OS and their manufacturing has evolved over the years. The discovery that the pituitary regulates gonadal function dates back from 1910, when studies in dogs revealed gonadal atrophy following partial ablation of the pituitary.[18] In 1929, Zondek found two hormones, secreted by the pituitary, Prolan A and B, now known as FSH and LH. Pregnant mare's serum gonadotropin (PMSG), extracted from pregnant mares' blood, was initially used for follicular stimulation in women as early as 1931,[19] but without achieving ovulation. Meanwhile, attempts were made to stimulate follicular development with pituitary extracts from several animal species, but this was complicated by antihormone antibody formation and inhibition of gonadotropin function. Human cadaver-sourced gonadotropins, on the contrary, were forced off the market because of their link with iatrogenic Creutzfeldt-Jakob Disease (iCJD).[20] Consequently, the process of extraction and purification of gonadotropins from other human sources was further improved and this led to the development of human menopausal gonadotropin (hMG), or menotropin, derived from the urine of menopausal women. Human menopausal gonadotropin is still one of the most widely used gonadotropins in ART.

Urinary gonadotropins

Urinary-derived gonadotropins were the only gonadotropins commercially available for ovulation induction (OI) and OS for more than 30 years.[21] Early preparations of human menopausal gonadotropin (hMG or menotropin) were only about 5% pure and contained, apart from some other impurities and protein contaminants, varying levels of FSH, LH, and hCG.[22,23] The purification techniques progressively improved and resulted, with the introduction of monoclonal antibodies against FSH, in a significant reduction in the content of unidentified protein contaminants lacking gonadotropin activity.[24] The highly purified urinary FSH preparations (uFSH-HP) now contain <0.1 IU LH and $<5\%$ unidentified urinary proteins.[25] Besides 'pure' uFSH preparations, highly purified hMG (HP-hMG) is available and widely used today, containing both FSH and LH activity.[26] However, most LH bioactivity

is provided by hCG, due to a mixture with urine from pregnant women, or added during manufacturing to reach the desired amount of LH-like biological activity (i.e. a process called 'spiking'; the usual preparations contain a 1:1 ratio of FSH to LH).[27] The enhanced purity of those products enabled the formulation of smaller injection volumes and subcutaneous, rather than intramuscular, administration.[28] At present, three types of urinary-derived gonadotropins are available: urinary FSH, hMG, and HP-hMG.

Recombinant FSH

In the late 1990s, by using recombinant DNA technology, an extremely pure (>99%) and potent alternative, recombinant FSH (rFSH) was produced, with minimal contamination by non-FSH materials. Recombinant gonadotropins can be produced in large volumes without variability in composition. This overcame the problem of a finite donor supply for urinary products. Another major advantage was the introduction of a pen injection device for subcutaneous administration, making it easier and less painful for women to self-administer the daily injections.

There are currently three rFSH products available on the market: follitropin alpha, follitropin beta, and follitropin delta. Both follitropin alpha and beta are produced in Chinese hamster ovary (CHO) cell lines, whereas follitropin delta is derived from a human fetal retinal cell line. A fourth variant, follitropin epsilon, is a fully human-cultured molecule with optimized glycosylation and is currently being studied.[29] Different biosimilar versions of follitropin alpha and beta have become available, even further enriching the gonadotropin market. Despite some disparities between follitropin alpha and follitropin beta, results of numerous clinical studies comparing the two products for OS in women undergoing IVF have shown no significant differences between the preparations in terms of efficacy and safety.[21] Dosing of follitropin delta is based on patients' ovarian reserve and bodyweight, decreasing the risk of excessive response and ovarian hyperstimulation.[30] This may be an appealing approach in expected high responders, but is obviously less relevant for the poor responder population.

Urinary versus *recombinant.* In response to the expansion and commercialization of rFSH, controversy arose with regard to the superiority of any type of gonadotropin, recombinant or urinary-derived. Despite improved purification techniques, urinary-derived FSH preparations contain low levels of contaminants, including LH. Although *in vitro* and animal models provided clear evidence of hormone-specific actions, solid proof of the same difference *in vivo* has not been clearly demonstrated.

Focusing on our goal to achieve the highest number of oocytes, it has been hypothesized that the purest and therefore most potent rFSH should be the gonadotropin of choice in the population of poor responders.[31] However, data on the comparison between urinary-derived and recombinant gonadotropins, specifically focusing on PORs, are scarce. Only one randomized controlled trial (RCT) has been published, comparing highly purified human menopausal gonadotropin (HP-hMG) with rFSH in 127 women of advanced reproductive age (⩾35 years), following downregulation.[32] More oocytes were obtained in the rFSH group ($p < 0.001$), but the proportion of transferrable top-quality embryos and LBR per started cycle trended toward improvement with HP-hMG [odds ratio (OR) = 1.3, 95% confidence interval (CI) = 0.9–1.8; OR = 1.9, 95% CI = 0.9–3.9, respectively], albeit differences were not statistically significant.

Meanwhile, a huge number of prospective, randomized trials on the comparison between recombinant and urinary gonadotropins has been published in an unselected IVF population. An updated meta-analysis in 2017 demonstrated superiority of the recombinant form of FSH in terms of number of oocytes ($p < 0.001$) compared with hMG.[33] However, looking merely at metaphase II oocytes (MII), this difference persisted only in the group treated with GnRH antagonist. Looking one step further even, to the number of embryos, it was no longer observed, and hMG offered the advantage over rFSH instead ($p = 0.001$). The implantation rate too was higher for hMG ($p = 0.03$). The ratio between FSH dose and the number of oocytes retrieved, however, was significantly lower in the FSH compared with the hMG group ($p < 0.001$). According to the ESHRE 2019 guidelines on OS, there is insufficient evidence to favor the use of one type of gonadotropin.[34]

So, based on current evidence, there might be superiority of rFSH in terms of number of

oocytes, but this is not translated into better reproductive outcomes. Small differences in certain POR subgroups cannot be ruled out based on the available literature.

Some authors have suggested an improved ovarian response for POR with a combination of rFSH with hMG or low-dose hCG, compared with traditional stimulation.[35,36] Conversely, some others failed to confirm these findings.[37–40] The concept of LH supplementation on OS is described below, but because there is no demonstrable superiority of one type of gonadotropin over another, combination therapy seems reasonless and expensive.

Long-acting FSH

Molecular engineering provided the technology to modify FSH preparations, prolonging their half-lives and therapeutic actions, thereby reducing the number of required injections. So, in terms of patient friendliness, the new long-acting FSH (corifollitropin alfa) offers an interesting alternative to daily injections of exogenous gonadotropins. First, results were promising, showing a potential increase in the number of oocytes in the general population using a GnRH antagonist protocol.[41] Nonetheless, in 2015, an RCT focusing on poor responders showed no significant difference in terms of cumulus-oocyte complexes (COCs) retrieved.[42] In a small pilot study in young poor responders fulfilling the BC, a possible trend toward higher ongoing pregnancy rate (OPR) was seen, when corifollitropin alfa was followed by daily injections of hMG.[43] Nonetheless, in 2017, in a large RCT in young Bologna POR, no difference in number of oocytes or OPR could be confirmed.[44]

Recombinant LH

All OS regimens involve exogeneous FSH administration. The question whether FSH alone is sufficient or a combination of gonadotropins could enhance outcome remains largely unanswered.

The rationale for LH supplementation comes from the knowledge on the physiology of the normal ovulatory cycle, where FSH and LH play in concert to stimulate folliculogenesis and subsequent ovulation. According to the 'two-cell-two-gonadotropin model', LH stimulates theca cells, thereby increasing androgen production, while FSH promotes the synthesis of estradiol through proliferation of granulosa cells (GCs). However, in the late stages of follicular development, GCs express LH receptors and further follicular growth seems to depend partially on the presence of LH.[45] As the role of LH is defined in the final phase of folliculogenesis, the theoretical benefit could lie in the quality of the oocytes, rather than in the absolute number of oocytes. However, the exact role of exogenous LH during OS remains controversial.[46] Because the introduction and widespread use of recombinant FSH as an alternative to hMG have not coincided with a decline in overall ART success rates, it has been stated that the presence of LH or hCG-driven LH activity apparently has no influence on success rates.[47] Next to hMG with its intrinsic LH-like activity, recombinant LH (rLH) on top of rFSH offers an alternative way of supplementing LH during OS.

Predicted poor responders. Different trials on the supplementation of rLH during GnRH antagonist stimulation, however, failed to show a clear benefit.[48,49] When it became clear that routine administration of LH did not positively influence chances in normal responders, focus shifted to POR. A meta-analysis in 2014, including 1129 ART cycles in POR patients, noted an increase in the number of retrieved oocytes (weighted mean difference + 0.75 oocytes, 95% CI = 0.14–1.36), and improved clinical pregnancy rates [relative risk (RR) = 1.30; 95% CI = 1.01–1.67].[50] Part of the 40 RCTs included predate the BC, so the heterogeneity of the trials makes the interpretation of the results difficult. In a large multicenter RCT in 2017, exploring the use of rLH in POR according to the BC in a long GnRH agonist (GnRHa) downregulation protocol, Humaidan and colleagues[51] observed no difference in neither implantation rate nor LBR. A *post hoc* analysis, on the contrary, showed a benefit for moderate and severe POR. An updated systematic review in 2018 concluded that a benefit exists for unexpected POR and women 36–39 years of age, while its added value in general POR population remains unclear.[52]

Unpredicted poor responders. Since the introduction of the Poseidon criteria, more focused and profound research is possible on the four subgroups of POR patients. The specific subgroup of normo-ovulatory normo-gonadotropic women termed 'hypo-responders' (Poseidon groups 1 and 2) demonstrate a certain ovarian resistance to gonadotropin stimulation, despite normal prestimulation

characteristics. This ovarian resistance can clinically manifest as an 'initial slow response' or 'stagnation' in follicular development during OS with FSH monotherapy.[53,54] This might indeed be the group of patients taking advantage of add-back LH therapy. Hyporesponsive women have a lower LBR compared with normal responding patients.[55] The pathophysiological mechanisms explaining this hypo-response are not yet fully understood. However, besides some environmental contaminants, such as, asynchronous follicular development, low gonadotropin starting dose, or technical issues, a polygenic trait involving gonadotropins and/or their receptors has been hypothesized as a plausible mechanism, at least partially explaining the phenomenon of reduced ovarian sensitivity.[56] For example, a study from 2016 demonstrated that the prevalence of hypo-response was higher in carriers of the serine variant in position 680 of an FSH-receptor (FSH-R) polymorphism than in wild-type haplotypes.[57] Similarly, a higher consumption of exogeneous gonadotropins has been observed in a specific polymorphism of the FSH R-promoter (A allele carriers compared with G allele carriers).[58] It has also been shown that differences in the endogenous LH molecule or specific LH-R polymorphisms could influence ovarian response during controlled ovarian stimulation (COS).[59,60] It is therefore plausible that this genetically determined resistance to exogeneous gonadotropins could be (at least partially) overcome by the addition of LH.

As there is no association between specific polymorphisms and prestimulation characteristics such as anti-Müllerian hormone (AMH) and/or antral follicle count (AFC), identification of suboptimal responders is only possible post factum. Despite the lack of solid evidence of the beneficial effect of LH supplementation in POR, it is already routinely implemented by a lot of clinicians in daily clinical practice.[61] Nevertheless, further prospective trials are required to prove and quantify the benefit of LH add-back in hypo-responders and potentially link the response to genetic polymorphisms.

Gonadotropins—dose

FSH dose increase

Not only the number of antral follicles present in the ovaries, but also the sensitivity of those follicles to FSH define the response to stimulation with gonadotropins. A daily dose of 150 IU is often promoted as an empirical 'normal' dose, although clear consensus on this topic is still lacking. With this dosage, a number of patients will develop a poor response. Most clinicians are tailoring the daily FSH dose based on prestimulation ORTs (AMH and/or AFC) in an attempt to prevent this condition. Dose adjustments might be even implemented to rescue an ongoing cycle with initial low response. The question is whether this 'individualized' approach always improves reproductive outcomes.

In a retrospective study, a total of 160 women with normal prestimulation characteristics, but a history of suboptimal response (four to nine oocytes retrieved) during fixed antagonist protocol, were recruited to receive an increase in rFSH in the subsequent cycle.[62] A dose increment seemed to result in a significantly higher number of oocytes (nine *versus* six, $p < 0.001$) and good quality embryos (four *versus* three, $p < 0.001$). Evidence from a small-scale RCT shows that also patients with an FSH-R polymorphism might benefit from a higher FSH starting dose. A dose of 225 IU FSH/day instead of 150 IU/day was able to restore estradiol levels at the end of stimulation of women homozygous for Ser/Ser at position 680 of the FSH-R gene to levels similar to those of women with wild-type genotype.[63] Whether this also results in better outcomes in terms of OPR, or even LBR, remains to be elucidated.

In predicted poor responders (POSEIDON groups 3 and 4) however, individualized dosing of FSH has a much lower chance of altering their fate.[64] Extremely high doses of gonadotropins have been used for decades in poor responder patients, increasing cost and treatment burden. Augmenting the dose of FSH beyond 300 IU/day does not contribute to any enhanced ovarian response though.[65,66] Today, it is clear that these patients have fewer recruitable follicles and that gonadotropins, independently of the dosage administered, only support the cohort of follicles sensitive to stimulation, without generating follicles de novo.

Mild OS

Mild OS has emerged as an alternative to high-dose ovarian stimulation (HDOS) or conventional IVF. Several investigators propose this as an equally effective alternative, offering advantages in

terms of patient friendliness and treatment cost.[67,68] Terminology of different types of mild stimulation IVF (MS-IVF) has been defined in a proposal statement from the International Society for Mild Approaches in Assisted Reproduction (ISMAAR).[69] A 'mild IVF cycle' is defined as 'the method when FSH or hMG is administered at lower doses, and/or for a shorter duration in a GnRH antagonist co-treated cycle, or when oral compounds (anti-estrogens, or aromatase inhibitors) are used, either alone or in combination with gonadotropins'.[69]

Natural cycle IVF. The first live birth after IVF was achieved in a purely natural cycle, without any exogeneous stimulation.[70] This was the method of choice for the first few years while IVF was still in its infancy. However, early attempts at IVF were associated with low efficiency. In natural cycle IVF, where an oocyte is retrieved from the dominant follicle formed during a woman's spontaneous cycle, cycle cancelation rate is high because of premature LH surge.[71] Chances of success are very low in Bologna poor responders and natural cycle IVF is therefore not the treatment of choice.[72]

Modified natural cycle IVF. Following the ISMAAR proposal on mild IVF, the term 'modified natural cycle' (MNC) should be applied 'when exogeneous hormones or any drugs are used when IVF is being performed during a spontaneous cycle with the aim of collecting a naturally selected single oocyte but with a reduction in chance of cycle cancellation'. This includes the administration of hCG to trigger final oocyte maturation, or the use of GnRH antagonist with or without add-back therapy of FSH or hMG.

In an RCT by Morgia and colleagues,[73] 129 PORs were randomized to either MNC or a conventional stimulation with micro-GnRH analog flare. Pregnancy rates per cycle and per transfer were low and comparable between the two groups. In a retrospective cohort study in 2019, including 476 advanced-age Bologna poor responders, there was no significant association between the type of treatment strategy (HDOS *versus* MNC-IVF) and the OPR.[74] Patients who fail to produce more than one or two oocytes in response to conventional OS therefore seem respectable candidates for MNC-IVF, especially as there are some advantages such as patient friendliness, reduced duration and dose of gonadotropins, and reduced overall cost per stimulated cycle.

So, in a specifically selected patient group, MNC offers a valuable alternative to HDOS and can be considered as an easy and rather cheap approach in the management of poor responders.[75] However, prognosis remains poor.

Mild IVF. In line with the MNC approach, there has been a renewed interest in the use of low dosages of gonadotropins (⩽150 IU/day) for mild stimulation in IVF protocols. There is still some skepticism among clinicians concerning pregnancy outcomes in mild OS in the general infertility population.[68] Poor responders with a diminished ovarian reserve, however, possibly do not benefit from high doses of gonadotropins. In the OPTIMIST study, there was no improvement in LBR in expected poor responders, comparing standard doses of FSH (150 IU/day) *versus* an increased FSH dose (225/450 IU/day). However, different questions on the interpretation of those data were raised by several authors[76–78] and the applicability to a wider practice was questioned. In a recent meta-analysis on RCTs by Datta and colleagues,[67] no difference in OPR or LBR was found between mild and conventional stimulation. Mild OS should therefore be considered in poor responders. However, not all poor responder patients are the same, so individualization remains crucial.[78] POSEIDON groups 3 and 4 are characterized by a low ovarian reserve, which translates into a poor prognosis.[79] These patients might not benefit from high-dose stimulation, given the very low functional ovarian reserve and could be eligible for mild IVF.

Oral compounds. Two oral drugs are frequently used during (mild stimulation) IVF, namely, clomiphene citrate (CC) and letrozole. CC is a selective estrogen receptor modulator (SERM) and acts by blocking hypothalamic estrogen receptors, thereby blocking the negative feedback effect of circulating endogenous estrogen and subsequently increasing the release of GnRH, FSH, and LH.[80] Letrozole is an aromatase inhibitor and reversibly binds and prevents aromatase from producing estrogens. Both medications are administered orally, typically starting on the third to seventh day of the menstrual cycle and are mainly used in anovulatory patients for OI.

The strategy of minimal stimulation protocols, with CC in the early follicular phase, was proposed as early as 1985.[81] Potential benefits of replacing the injectable and expensive FSH by these oral agents are to reduce the costs of the therapy and minimize the number of injections needed, without hampering the reproductive outcomes. A prospective cohort study in 2015 showed that this approach offered a few advantages such as a positive influence on the endometrial receptivity, and reduced risk of ovarian hyperstimulation syndrome (OHSS), but deliberately only included good prognosis patients, on the assumption that these were the patients possibly benefiting from this milder approach.[82] Several retrospective and prospective studies have compared outcomes between conventional stimulation and mild OS with both oral agents in POR.[66,83,84] A meta-analysis in 2017, including 22 studies, compared conventional stimulation with OS using CC and/or letrozole.[85] Considering expected poor responders, reproductive outcomes were similar, but ART cycles using CC have a reduced FSH consumption and therefore cost-benefit advantages on conventional treatment.

Conclusions

The Poseidon criteria seem to offer a convenient system, where valid information can be obtained concerning a specific and fairly homogeneous population. At this point, however, it remains to be elucidated whether optimizing treatment modalities in a specific subgroup can improve reproductive outcomes. Future clinical trials should study the four groups individually, aiming to discover the ideal clinical management for each group.

Looking at efficacy and safety, there is insufficient scientific evidence to favor the use of one type of gonadotropin over the other. Decisions on the type of gonadotropins are therefore still mainly based on clinician's experience and preference, local availability, cost, and convenience. In the future, pharmacogenomics may predict OS success and guide decision-making on the design of the treatment and adjustment of doses. LH supplementation could be specifically reserved for patients with gonadotropin or gonadotropin receptor polymorphisms with known decreased ovarian sensitivity.

Dosage of gonadotropins should be individualized. Whereas patients with a predefined low ovarian reserve could have similar outcomes with a milder approach, the cohort of suboptimal responders might benefit from an increased dose of FSH or the addition of LH.

Taking into account the disappointing results, based on an increased aneuploidy rate, in older poor responders irrespective of the treatment administered, research focus should probably lie on younger patients, where different treatment modalities could still have a real impact on the outcome.

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ORCID iD


Liese Boudry https://orcid.org/0000-0003-3175-2996

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