Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, Sunde A, Schmidt L, Cooke ID *et al.* The international glossary on infertility and fertility care, 2017. *Hum Reprod* 2017;**32**:1786–1801.

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Reply: The low responder according to the POSEIDON criteria: is the prognosis really poor?

Sir,

With interest we read the Letter to the Editor by Esteves on behalf of the Patient-Oriented Strategies Encompassing Individualize D Oocyte Number (POSEIDON) group. Various points were raised by the author regarding the significance of the POSEIDON classification of low responders in terms of prognosis for a live birth and its value to guide clinical management in low-prognosis women. We respectfully do not share the author's concerns about our understanding of the POSEIDON classification nor about the significance of the findings in the Leijdekkers article. Our evaluation of the cumulative live birth rates over 18 months of treatment initiates the essential validation of the POSEIDON criteria and provides relevant information about the long-term pregnancy prospects of the various subgroups of women, especially considering the fact that a large proportion will have more than one IVF/ICSI treatment cycle (Leijdekkers *et al.*, 2019).

In the letter, the author refers to an article by Alviggi, in which the follicle-to-oocyte index (FOI) is introduced to explain the nature of the subset of patients with an adequate ovarian reserve and a poor or suboptimal response to stimulation (Alviggi *et al.*, 2018). This article extensively addresses a low FOI as being a clinical condition that would express a state of reduced follicle sensitivity to exogenous FSH. However, the exact pathophysiology is still poorly understood, and its significance in terms of effects on live birth rates has not been properly evaluated. Therefore, at this point, it remains to be elucidated whether optimizing the FOI will improve reproductive outcomes. In our opinion, well-powered randomized controlled trials (RCTs) first have to reveal a beneficial impact on cumulative live birth rates of interventions that maximize the FOI, including the suggested individualization of ovarian stimulation, before clinical management can be guided by the POSEIDON criteria. Available studies that evaluated the individualization of ovarian stimulation by increasing the FSH dosage have so far all failed to reveal an increase in live birth rates despite the higher number of retrieved oocytes (Arce *et al.*, 2014; Lensen *et al.*, 2018). Therefore, the putative causal relation between the number of oocytes or embryos and the chance of a live birth may require reconsideration.

Additionally, the author refers to another article, to explain the concept of low prognosis that was introduced by the POSEIDON group (Esteves *et al.*, 2018). In this article, a tabulation was presented of studies that assessed the prognosis of low responders according to the Bologna criteria. These studies were mostly done in women aged ≥40 years and revealed very low per cycle live birth rates. This group of women could be considered to be the real low prognosis group, in full agreement with the intention of the Bologna system. In the same article, the POSEIDON criteria were explained as a potential improvement of the Bologna system in order to 'allow the clinician to classify patients who have a low prognosis in artificial reproductive technologies (ART), and to prepare a stimulation plan aiming at reaching the number of oocytes needed to obtain at least one euploid blastocyst for transfer.' As was done for the Bologna criteria (Busnelli *et al.*, 2015; La Marca *et al.*, 2015; Bozdag *et al.*, 2017), our group used a prospective dataset that accurately reflects the Dutch ART population, to assess how poor the prognosis of the POSEIDON subgroups really is in daily practice. Using the exact POSEIDON criteria, we could study the cumulative live birth rates (CLBR) over a treatment period of 18 months, making the data unique. Hereby, our study surpassed the stage of looking at the number of oocytes or the ploidy status of embryos, as these intermediate outcomes do not mean so much from the couple's perspective.

Unfortunately, the author shed doubt on such assessment of the cumulative chance of a live birth within a time frame of 18 months of IVF/ICSI treatment. Instead, the use of the ICMART (International Committee for Monitoring Assisted Reproductive Technologies) definition was suggested (Zegers-Hochschild *et al.*, 2017). Per cycle results following the ICMART definition ('the number of deliveries with at least one live birth resulting from one initiated or aspirated ART cycle, including all cycles in which fresh and/or frozen embryos are transferred, until one delivery with a live birth occurs or until all embryos are used, whichever occurs first') are presented in table III of our article and are in line with the cumulative live birth findings. For the 18 month follow-up, we do not consider inflation of the CLBR due to dropouts to be an issue, as these rates reflect the long-term, real-life outcomes for the POSEIDON subgroups. Moreover, we carefully addressed the issue of treatment discontinuation by using the optimistic and conservative analytic approach, ensuring the robustness of our findings. We strongly consider the evaluation of the long-term pregnancy prospects to be more informative for our patients, as a large proportion will have more than just one treatment cycle. The author may be right that case numbers are always too low. We therefore consider our article to be an invitation to confirm and thereby reinforce our observations or else to refute them by using scientific data.

Furthermore, the author wishes to demonstrate that CLBR per cycle are lower in the POSEIDON classes compared with normal responders. There is no doubt that this is true. Our article, however, focuses on the longer term, real-life outcome for couples, as IVF/ICSI treatment is often repetitive. Repeated cycles will create accumulation of pregnancy chances and reveal the actual prospects that couples will get from investing time and effort to go through all the steps necessary to finish several full treatment cycles. When observing the cumulative outcome after 18 months in the various POSEIDON subgroups, we have to conclude that the prognosis is not very poor, which is precisely the message of our work. We understand Esteves' desire to achieve higher reproductive outcomes for women initiating IVF/ICSI, but what is reproductive outcome and where is the proof that optimizing the FOI improves this reproductive outcome?

Today, no evidence supports the use of, for instance, higher FSH dosages to improve this intermediate outcome. Many therapeutic options to improve oocyte yield for unexpected low responders have been presented (Drakopoulos *et al.*, 2018), but without convincing evidence that the chance of having a baby is increased. The putative causal relation between oocyte number and cumulative live birth rates needs to be confirmed by randomized trials, and the available evidence does not indicate any efficacy gain (Arce *et al.*, 2014; Lensen *et al.*, 2018). For the expected low responder, increasing the FSH dosage is irrational, but which other pharmacological interventions should one think of that will improve the chances to conceive? And moreover, what is the difference between oocyte/embryo accumulation (Vaiarelli *et al.*, 2018; Xu *et al.*, 2018) and cumulative repeated cycles as presented in our article. An RCT is needed to compare these two approaches and provide evidence for the author's claim that 'individualization of the ovarian stimulation is superior to a "one size fits all" policy in POSEIDON patients'. At this point, using the new criteria to guide clinical management thus seems to be a bridge too far.

In summary, we feel that Esteves *et al.* (2018) may have misunderstood the intentions of the Leijdekkers article: providing robust information on the real-life ART prognosis for the women in various POSEIDON subgroups. The surprising results may make it necessary for us all to rethink the value of the POSEIDON system as a low prognosis classification.

Conflict of interest

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References

Alviggi C, Conforti A, Esteves SC, Vallone R, Venturella R, Staiano S, Castaldo E, Andersen CY, Placido GD. Understanding ovarian hypo-response to exogenous gonadotropin in ovarian stimulation and its new proposed marker-the follicle-to-oocyte (FOI) index. *Front Endocrinol (Lausanne)* 2018;**9**:589.

Arce J-C, Nyboe Andersen A, Fernández-Sánchez M, Visnova H, Bosch E, García-Velasco JA, Barri P, Sutter P, de Klein BM, BCJM F. Ovarian response to recombinant human follicle-stimulating hormone: a randomized, antimüllerian hormone–stratified, dose–response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril* 2014;**102**:1633–1640 e5.

Bozdag G, Polat M, Yarali I, Yarali H. Live birth rates in various subgroups of poor ovarian responders fulfilling the Bologna criteria. *Reprod Biomed Online* 2017;**34**:639–644.

Busnelli A, Papaleo E, Prato DD, Vecchia IL, Iachini E, Paffoni A, Candiani M, Somigliana E. A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria. *Hum Reprod* 2015;**30**:315–322.

Drakopoulos P, Santos-Ribeiro S, Bosch E, Garcia-Velasco J, Blockeel C, Romito A, Tournaye H, Polyzos NP. The effect of dose adjustments in a subsequent cycle of women with suboptimal response following conventional ovarian stimulation. *Front Endocrinol (Lausanne)* 2018;**9**:361.

Esteves SC, Roque M, Bedoschi GM, Conforti A, Humaidan P, Alviggi C. Defining low prognosis patients undergoing assisted reproductive technology: POSEIDON criteria—the why. *Front Endocrinol (Lausanne)* 2018;**9**:461 Frontiers.

Leijdekkers JA, Eijkemans MJC, Tilborg TC, van Oudshoorn SC, RJT G, van Hoek A, Lambalk CB, Bruin JP, de Fleischer K, Mochtar MH *et al.* Cumulative live birth rates in low-prognosis women. *Hum Reprod* 2019;**4**:1030–1041.

Lensen SF, Wilkinson J, Leijdekkers JA, Marca AL, Mol BWJ, Marjoribanks J, Torrance H, Broekmans FJ. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). *Cochrane Database Syst Rev* 2018;**2**:CD012693.

Marca AL, Grisendi V, Giulini S, Sighinolfi G, Tirelli A, Argento C, Re C, Tagliasacchi D, Marsella T, Sunkara SK. Live birth rates in the different combinations of the Bologna criteria poor ovarian responders: a validation study. *J Assist Reprod Genet* 2015;**32**:931–937.

Vaiarelli A, Cimadomo D, Trabucco E, Vallefuoco R, Buffo L, Dusi L, Fiorini F, Barnocchi N, Bulletti FM, Rienzi L *et al.* Double stimulation in the same ovarian cycle (DuoStim) to maximize the number of oocytes retrieved from poor prognosis patients: a Multicenter experience and SWOT analysis. *Front Endocrinol (Lausanne)* 2018;**9**:317.

Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, Wang S. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol* 2018;**16**:29.

Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, Mouzon J D, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke ID *et al.* The international glossary on infertility and fertility care, 2017. *Hum Reprod* 2017;**32**:1786–1801.

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