than 150 IU FSH daily in 'poor responders' embarking on IVF/ICSI treatment is not effective in terms of increasing the LBR.

Although we recognize the amount of time and dedication spent to conduct this large clinical trial which challenges the concept of individualized controlled ovarian stimulation (iCOS), we firmly believe that the conclusion of this publication is quite misleading as the term 'poor responder' is inappropriately used for a population that certainly does not fulfill neither the established ESHRE Bologna POR criteria (Ferraretti *et al.*, 2011) nor the recently suggested POSEIDON criteria for predicted POR (Humaidan *et al.*, 2016). Many previous publications pointed out the misleading results deriving from multiple studies using multiple POR definitions (Polyzos and Devroey, 2011), and of course, we acknowledge the fact that the study by van Tilborg *et al.* was designed prior to the establishment of the Bologna criteria. Nevertheless, we are surprised that apparently no reviewer commented on the confusion of terms and the subsequent misleading advice regarding the clinical management of the POR patient.

Prior to the study by van Tilborg *et al.*, best clinical practice has been based on large cohort studies, stratifying patients into poor responders (<4 oocytes retrieved) and sub-optimal responders (4–9 oocytes retrieved), and for both groups it was clearly stated that retrieving more oocytes significantly increases the cumulative LBR (Sunkara *et al.*, 2011; Drakopoulos *et al.*, 2016). Hence, the current policy is to adopt ovarian reserve tests, AFC and/or AMH, to tailor the treatment, aiming at the retrieval of as many oocytes as possible in predicted hypo-responder patients. This policy is now challenged by two large RCTs (Nyboe Andersen *et al.*, 2017; van Tilborg *et al.*, 2017), which could not find an increase in LBR, despite the fact that iCOS resulted in significantly fewer poor responses in both studies (<4 or 5 oocytes retrieved, respectively). However, these studies did not investigate POR patients according to the established definitions, but rather sub-optimal responders. Thus, sub-analysis according to the established POR definitions, including sub-stratifications by age, should be performed before drawing conclusions regarding clinical management.

Secondly, we suggest that a daily FSH dose above 300 IU does not add any additional benefit in terms of ovarian response (Berkkanoglu and Ozgur, 2010), apart from increasing the cost and, thus, the difference in consumption and cost between the individualized dosing group and the standard dosing group. Furthermore, the reader is not informed about the ratio of rFSH and uFSH used during the trial—and for which groups. We raise this issue as this might also have introduced a response bias, taking into account the physiological difference in isoform profiles between rFSH and uFSH (Yding Andersen, 2002). Moreover, what was the basis of an 18-month follow-up period, instead of follow-up after the use of all cryopreserved embryos?

Finally, there seems to be a discrepancy between the trial protocol (Dutch trial register NTR2657) and the publication. According to the register, patients with AFC = 7 were administered 225 FSH IU daily whereas in the publication it was stated that these patients were administered 450 IU/day?

Conflict of interest

P.H. and S.C.E. are board members of the POSEIDON group, www.groupposeidon.com. P.H. received unrestricted research grants from MSD, Merck, and Ferring as well as honoraria for lectures from MSD, Merck and IBSA. S.C.E. received honoraria for lectures from Merck, Besins, and Lilly. T.H. reports no conflicts of interest.

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doi:10.1093/humrep/dey059

Advanced Access Publication on February 8, 2018

Derailing individualized ovarian stimulation

Sir,

We read with interest the paper by Tilborg that incorporated a *post hoc* analysis of the utility of anti-müllerian hormone (AMH) for a cost-effectiveness analysis (van Tilborg *et al.*, 2017). The authors predicated the randomized control trial (RCT) and individualization of dose solely

on antral follicle count, but there are a number of substantial issues that question the ability to retrospectively draw conclusions on the utility of AMH to individualize treatment. Specifically, longitudinal measurement of serum AMH shows during GnRH-agonist downregulation shows marked and clinically relevant changes, an effect dependent on the duration of GnRH-agonist treatment (Su *et al.*, 2013, Drakopoulos *et al.*, 2017). Therefore, serum AMH level should be measured before start of GnRH-agonist downregulation and not once started, as performed by Tilborg and colleagues. Secondly, four AMH categories have been developed, but is unclear what modelling underlies these thresholds. Particularly AMH of 1.33 to <2.25ng/ml (9.5–18.0 pmol/l) was used to classify normal responders, but in recent phase II (Arce *et al.*, 2014) and phase III RCTs (Nyboe Andersen *et al.*, 2017), a poor response to ovarian stimulation was anticipated with AMH values <15.0 pmol/l (<2.1 ng/ml) (Arce *et al.*, 2014). Thirdly, retrospectively predicting the outcome of individualization of treatment based on AMH assumes equivalence with AFC in their association with oocyte yield. In contrast to older meta-analyses, several recent multicentre studies demonstrate that AMH exhibits an almost two-fold higher correlation coefficient with oocyte yield than that observed for AFC determined across multiple sites (Nelson *et al.* 2015) and substantially lower variability (Anderson *et al.*, 2015). The variability between trial sites in AFC (or indeed in AMH) for the current study is not presented. Lastly, the authors use statistical methodology to predict the outcome for the 24% of women where AMH and AFC were discordant. However, this model incorporates the applied FSH dose which was based on the AFC but not on AMH, and the assumption that *post hoc* modelled predictions can replace real clinical outcomes is questionable. Collectively, these concerns would suggest that, rather than retrospectively infer conclusions about the utility of AMH for individualizing treatment from incorrectly timed samples, evidence from a large scale prospective international multicentre RCT should be used (Nyboe Andersen *et al.*, 2017).

Conflict of interest

S.M.N. has participated in Advisory Boards and received speakers fees from Beckman Coulter, Besins, Ferring, Finox, Merck, MSD and Roche Diagnostics. He has received research material and research grants from Beckman Coulter, Roche Diagnostics and Ferring. R.A.A. has participated in Advisory Boards and/or received speakers fees from Beckman Coulter, IBSA, Merck and Roche Diagnostics. He has received research support from Roche Diagnostics, Ansh labs and Ferring.

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doi:10.1093/humrep/dey060

Advanced Access Publication on February 8, 2018

Usefulness of individualized FSH, LH and GH dosing in ovarian stimulation of women with low ovarian reserve

Sir,

We read with interest the multicentre prospective study by van Tilborg *et al.* (2017) concluding that individualized FSH dosing, based on antral follicle count (AFC), does not improve live-birth rates or reduce costs as compared to a standard FSH dose. This is likely to be true for women with predicted normal response to controlled ovarian hyperstimulation (COH). As to hyper-responders, individualized FSH dosing appeared to reduce the risk of mild and moderate ovarian hyperstimulation syndrome (OHSS). On the other hand, the conclusions related to low and extremely low responders are not clear.

First of all, values of anti-Müllerian hormone (AMH) were included only retrospectively and were not taken into account in the decision about patients' eligibility. Yet, AMH, together with AFC, is an important predictor of poor ovarian reserve (Ferraretti *et al.*, 2011). Moreover, the lower limit of AFC for patient inclusion is not mentioned, and the authors admit that AFC evaluation may have been subject to inter-observer variability (van Tilborg *et al.*, 2017). It is thus important to make clear that their conclusions cannot be applied to women with poor and extremely poor ovarian reserve.