PLCζ is believed to occur during the early stages of gamete fusion, and thus before the sperm tail is incorporated into the oocyte. Thus, our figure represents a specific temporal stage of fertilization and not the entire sequence of events. It would, therefore, be inaccurate and misleading to have shown the sperm tail incorporated into the oocyte at this stage. While we are content with the fact that Fig. 2 (Kashir et al., 2010) was indeed a correct representation of a specific temporal stage of fertilization, and we agree with Ramalho-Santos that specific attention is required in future publications with regard to the precise positioning of the sperm tail, we recommend that authors also need to place significant consideration upon temporal aspects of the specific physiological and molecular events being described in order to minimize the risk of reader misinterpretation.

References


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The definition of ‘poor response’: Bologna criteria

Sir,

We read with interest the article entitled “ESHRE consensus on the definition of ‘poor response’ to ovarian stimulation for in vitro fertilization: the Bologna criteria” published in the July 2011 issue of Human Reproduction (Ferraretti et al., 2011). In the Abstract section, the authors state that “the definition presented here represents the first
realistic attempt by the scientific community to standardize the definition of poor ovarian response (POR) in a simple and reproducible manner. This statement is also repeated in the Conclusion section. Unfortunately, this is not the case. In 2005, we published our work entitled ‘Defining poor responders in assisted reproduction’ in a refereed journal, listed in all important literature search databases (PubMed, EMBase, etc.) (Sallam et al., 2005). However, our work was not mentioned in the list of references.

In our work, we attempted to define ‘poor responders’ as those patients from whom the number of oocytes retrieved leads to a significant decrease in the clinical pregnancy rate (Sallam et al., 2005). We analyzed the results of 782 IVF, ICSI and ICSI–testicular sperm extraction (TeSE) treatment cycles. In addition to regression analysis and the calculation of sensitivity and specificity, receiver-operator characteristic (ROC) curves were constructed in order to determine a critical number of oocytes retrieved, below which the clinical pregnancy rate was significantly diminished. The clinical pregnancy rate started to become significantly lower when fewer than five, six and eight oocytes were retrieved from patients treated with ICSI, IVF or TeSE/ICSI, respectively. We concluded that the definition of poor responders in assisted reproduction depends on the treatment modality and that poor responders are patients undergoing treatment with ICSI, IVF or TeSE/ICSI from whom fewer than five, six or eight oocytes are retrieved, respectively.

In addition to our objection to ignore our work all together, the current ESHRE consensus is vague and not exactly evidence-based. It defines POR on the presence of two of the three criteria. The first criterion is an advanced maternal age and an arbitrary cut-off point of 40 years was taken. Although we agree with the authors that maternal age definitely affects the outcome of assisted reproduction, they do not tell us how this figure of 40 years was reached and whether it was based on ROC curves using any institutional, national or international database of IVF/ICSI results (ASRM-SART, ICMART, etc.). For example, Al-Azemi et al. (2011) constructed such ROC curves in a group of 356 unselected women undergoing ovulation induction/IVF and found that the cut-off value was 35 years for pregnancy outcome and 36 years for poor response (Al-Azemi et al., 2011). The second criterion used is a previous POR defined as ≤3 oocytes with a conventional stimulation protocol.

The authors state that this figure was reached because it is the most frequently used in the literature. This can only be classified as Grade C evidence and the cut-off value should be reached by constructing ROC curves as performed in our study using an existing national or international database. The third criterion used is an abnormal ovarian reserve test where ranges of values rather than cut-off points are used, i.e. an antral follicle count of 5–7 follicles or a plasma anti-Müllerian hormone level between 0.5 and 1.1 ng/ml. Definite cut-off points would have been preferable and we agree with the authors that these should be extreme and based on ROC curves (Kwee et al., 2007; Elgindy et al., 2008; La Marca et al., 2010).

In our opinion, evidence-based principles require that calculating cut-off levels be based on ROC curves. We are therefore urging the ESHRE consensus group to re-consider this definition in light of evidence. We are also interested to know why our work was not referred to by the authors: was it because their search of literature was done hastily or because they have serious evidence-based objections to our work published in 2005 (which could have been discussed in their paper)?

### References


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### Reply: The definition of ‘poor response’: Bologna criteria

Sir,

We thank Dr Sallam et al. for their letter, but have to conclude that, unfortunately, the purpose of our paper (Ferraretti et al., 2011) may not have been clear to them. We welcome the opportunity to provide clarification.

First, they state that they published a ‘definition of poor responders’ before us, and therefore that our article is not the ‘first realistic attempt’ to reach a Consensus on the topic. We consider that their paper (Sallam et al., 2005) represents a retrospective analysis aiming at identifying the critical number of oocytes below which the pregnancy rate significantly decreases. In other words, it can be said that it aims to define a ‘low response’ in relation to pregnancy chances. Since many units have performed similar retrospective analysis, aiming to identify their own cut-off value, the literature is rich with controversial data on this issue, which has been underlined both in our article and by the first author of the letter as he underlined in the chapter in the book *Infertility and Assisted Reproduction* (Sallam et al., 2008).

The aim of the ESHRE consensus was to standardize criteria able to identify homogeneous populations of poor responders to be tested in future trials, and not to identify the ‘number of eggs’ which may define