Reply: Ovarian reserve screening: a scientific and ethical analysis

Sir,

We thank the correspondents for their interest in our paper and would like to respond to their comments. Professor Findlay et al. appear primarily to object to our suggestion that serum anti-Müllerian hormone (AMH) and ultrasound assessed antral follicle count (AFC) are valid screening tests of ovarian reserve, since neither AMH nor AFC directly measure ovarian reserve. Ovarian reserve has been defined as the remaining pool of non-growing follicles in the ovary at any given age (Kelsey et al., 2012; Findlay et al., 2014). Since AMH is principally produced by antral follicles of up to 10 mm in size (Jeppesen et al., 2012), the same population quantified as AFC by ultrasound assessment, we of course agree that neither AMH nor AFC can strictly speaking be seen as direct measures of ovarian reserve (non-growing primordial pool). However, we argue that such semantic distinctions between direct and indirect measures of ovarian reserve are not particularly helpful clinically, and certainly were not the focus of our paper.

We respectfully disagree with the correspondents’ view that it is inappropriate to refer to AMH and AFC as valid screening measures of ovarian reserve. Firstly, studies have shown highly significant positive correlations between serum AMH and AFC counts and ovarian reserve assessed by manual stereological counts of non-growing follicles in ovarian tissue samples (Hansen et al., 2011; Kelsey et al., 2012). Indeed, one of the correspondents has previously reported that serum AMH correlates very well \( r = 0.83 \) with histologically assessed ovarian reserve during the reproductive years (Kelsey et al., 2012). Therefore, while both AMH and AFC are both indirect measures of ovarian reserve, they still are biologically and clinically relevant ‘surrogate markers’ of ovarian reserve. While we understand that distinctions between direct and indirect measures of ovarian reserve are of significant importance to scientists working in the field, they are of much less importance to the practicing clinician. Furthermore, since it is presently impossible to directly assess non-growing primordial follicle numbers in vivo, without recourse to harmful and ethically prohibited practices such as ovarian biopsy, we can see no alternative clinical approach than using indirect measures of ovarian reserve such as AMH and AFC.

The correspondents go on to suggest that follicles measured by AMH or AFC should be classified as ‘ovulatory potential’, as distinct from ‘ovarian reserve’. While we agree that ‘ovulatory potential’ has significant merit in the context of controlled ovarian hyper-stimulation (COH), we do not think that the term ‘ovulatory potential’ is a useful description outside of the IVF context. For example, outside of COH only one follicle from this cohort of antral follicles will become dominant and actually reach maturity and ovulate, irrespective of whether the woman has a high or low antral follicle count. Therefore, two individuals with vastly different numbers of antral follicles, and contrasting ovarian reserve status, will still have exactly the same ovulatory potential—just one mature oocyte. As such we believe that the term ‘ovulatory potential’ is potentially confusing and therefore not ideal in a non-IVF setting. Secondly, the vast majority of researchers and clinicians alike, including those recognized as being eminent in the field (Toner and Seifer, 2013; Broer et al., 2014; Kushnir et al., 2014), currently refer to AMH and AFC as valid markers of ovarian reserve, even though they are certainly all aware that AMH and AFC are only indirect measures of ovarian reserve. As such, we can see little advantage in changing this established precedence and moving to the new term ‘ovulatory potential’.

Finally the correspondents suggest that due to technical issues with assessment of AMH and AFC (assay methodology, inter-observer variability, fluctuations during life course and multiple confounders such as the use of contraceptives and health issues), neither AMH nor AFC can be seen as a valid measures of ovarian reserve. While we acknowledge that ovarian reserve assessment by AMH and AFC is made more difficult due to these multiple confounders, we do not believe that this invalidates non-invasive assessment of ovarian reserve. Doctors interpreting results of ovarian reserve testing must simply be fully aware of the impact that these important confounders have on AMH and AFC levels, making appropriate risk adjustments as appropriate.

In conclusion, while we absolutely agree with the correspondents that AMH and AFC are not direct measures of the size of the primordial follicle pool, we still believe that AMH and AFC are the best available indirect measures of ovarian reserve status.

References


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doi:10.1093/humrep/dev009

Advanced Access publication on January 30, 2015