Ovarian reserve screening: a scientific and ethical analysis

Sir,

In a recent article, Tremellen and Savulescu (2014) ‘argue in support of screening the general population for diminished ovarian reserve (OR)’. They state that OR ‘is determined by the net result of the initial size of the primordial follicle endowment, the natural rate of atretic loss and the impact of any insult that may hasten follicle depletion’. However, OR is not defined, nor do they mention that OR is influenced by the rate at which primordial follicles are activated and leave the primordial follicle pool. They remark that anti-Müllerian hormone (AMH) and antral follicle count (AFC) are excellent quantitative markers of OR, but possibly do not reflect oocyte quality and therefore the chances of immediate natural conception. However, a poor AMH or AFC result does reflect a marked reduction in the chances of IVF-related conception.

We support the call for methods to determine the OR as a means of informing women about their likely future fertility and reproductive lifespan, particularly those with a markedly reduced OR. It is not our purpose here to comment on the practical or ethical issues of screening for OR, but there is a need for critical analysis of what is meant by the term OR and the limitations of the use of AMH or AFC as a measure of it.

In a recent paper (Findlay et al., 2014), we argue that the term ‘ovarian reserve’ should be confined to the primordial pool of follicles. AMH and AFC only measure the pool of growing antral follicles and not the actual size of the primordial pool, and as such reflect the potential for production of oocytes within a relatively short (6 month) period of time. We propose that the follicles measured by AMH or AFC should be classed as ‘ovulatory potential’ as distinct from ‘ovarian reserve’. It is important to remember that primordial follicles do not produce AMH and cannot be detected by ultrasound. The use of serum AMH as a measure of the size of the primordial pool is based only on a correlation between a histological assessment of primordial follicle number in the ovary and the level of AMH in healthy adult women (Hansen et al., 2011). At present, we do not have a method other than histological analysis, of measuring directly the size of the primordial pool of follicles.

The basis of the confusion about the meaning of OR and its influence on fertility most probably reflects the different interpretations by clinicians, scientists and the general public of what is meant by the ‘ovarian reserve’. We believe that agreeing on what we mean by terms like OR should be clear and consistent so as not to confuse researchers, clinicians, the media and women about their future fertility and likelihood of pregnancy. While we strongly believe that the term ‘ovarian reserve’ should be confined to the pool of primordial follicles, we are open to debate about how to define the cohort of growing antral follicles detected by AMH or AFC in terms of future fertility. We suggest ‘ovulatory potential’ (Findlay et al., 2014), highlighting both the potential of those follicles to develop further to ovulatory status (as, for example, in assisted conception) and their transient nature. Tremellen and Savulescu (2014) propose ‘total fertility potential’, which would appear to include the primordial pool of follicles.

In addition to confusion about the meaning of OR, there are limitations to using serum AMH as a measure of the ‘total fertility potential’, as defined by Tremellen and Savulescu (2014). Problems with AMH assay methodology have been reviewed recently by Dewailly et al. (2014). There are at least as many great issues with AFC measurement (Iliodromiti et al., 2014). There is enormous variability in AMH levels between individuals of the same age (Kelsey et al., 2011) and little prospective data assessing changes over time in individual women, although overall there does seem to be a relationship to time to menopause (Tehrani et al., 2013). Tremellen and Savulescu (2014) point out the influence of oral contraceptives on serum AMH levels; there is growing evidence that a wide range of health and endocrine factors can also impact AMH, complicating interpretation (Lawrenz et al., 2012; Su et al., 2013; Titus et al., 2013; van Dorp et al., 2014). Interpretation further requires recognition of the changing relationship between AMH and ovarian function through puberty, adolescence and early adulthood.

In conclusion, whilst we recognize the potential value of a screening tool for OR for reproductive aged women, we emphasize that a test to measure OR does not currently exist. We look forward to further debate on the definition of the OR and the methods to assess it.

References


van Dorp W, van den Heuvel-Eibrink MM, de Vries AC, Pluijm SM, Visser JA, Pieters R, Laven JS. Decreased serum anti-Mullerian hormone levels in girls assessed by manual stereological counts of non-growing follicles in 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 or AFC can be seen as a valid measure 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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