INVITED COMMENTARY

The Flat Earth Society: a rose by any other name?

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In the current issue of Human Reproduction van Dorp et al. (2013) provide us with seminal evidence about a serum marker that purportedly informs us about current and future ovarian function. Current dogma attributes to this marker the ability to determine the number of primordial follicles remaining in the ovary. The findings in this publication force us to reconsider this long-held view. I congratulate the authors for testing hypotheses that challenge current dogma. I also applaud the authors for employing scientifically accurate terminology in their report.

In a cross-sectional study the authors examine serum AMH levels in 208 girls with newly diagnosed cancer who are attending a cancer center. They compare the findings with a control group of 250 age-matched healthy girls. The seminal finding is that, in young girls with cancer, serum anti-Müllerian hormone (AMH) levels correlate significantly with temperature, C-reactive protein and hemoglobin. The investigators show that AMH levels correlate with impairment of these surrogate markers of general health status in girls. The seminal point is other factors may well influence serum AMH levels besides the number of pre-antral follicles in the ovary. The authors correctly point out that the lower serum levels of AMH in these girls may be due to reduced AMH production by individual follicles as a result of follicle dysfunction related to the chronic disease. To me this seems to be the most biologically plausible explanation. However, the authors also point out that a reduced number of primordial follicles in young girls with cancer could be another explanation. However, I’m not clear on the proposed mechanism(s) that would lead to this in young girls with cancer. I would be interested in hearing their ideas. Perhaps impaired general health induces apoptosis in primordial follicles by some mechanism?

It’s always a pleasure to read ground-breaking research with hard evidence that challenges current dogma. When new insights like this seep into our consciousness, it is important that we re-evaluate the scientific language that we have been using under the old paradigm and ask ourselves an important question. Do we need to change how we talk about the issues here? Are we at risk of becoming members of the Flat Earth Society by continuing to use scientifically inaccurate terminology? Should we conclude that a rose by any other name smells as sweet, so there is no need for change? Does it really matter how we use our scientific terms?

Don’t get me wrong. I totally agree with Juliet’s line in William Shakespeare’s Romeo and Juliet, ‘That which we call a rose by any other name would smell as sweet’ (www.bartleby.com). I have a caveat, however.

I am reminded that Juliet is referring to the esthetics of the rose. She is not making a scientific statement to inform us about the chemical composition of aromatic hydrocarbons in the blossom. The lady is not describing olfactory receptor neurons in the nose that interact with said hydrocarbons. Young and lovely Juliet is not elucidating the mechanism by which neural networks in our cerebral cortex create the pleasing effect of the aroma on our mood.

Esthetic language is one thing. Scientific language is another. I am reminded that in the field of scientific research accurate and specific terminology plays a critical role in our ability to communicate new findings, relate these findings to bigger picture implications and conceive new hypotheses to be tested, assuming the new findings are indeed correct. Not infrequently new scientific findings require a redefining of the terminology that we use in specific scientific domains. This sometimes leads to clashes between opposing forces that can destroy relationships and longstanding friendships. Witness the fact that the Flat Earth Society still argues their position (Wolchover, 2012).

What’s in a name? I was heartened to see that the authors refrained from using the term ‘diminished ovarian reserve’ in their report. Rather, they refer to ‘decreased serum anti-Müllerian hormone levels.’ The term ‘diminished ovarian reserve’ of course has been used for many years to refer to the number of primordial follicles remaining in the ovary. The fact is we currently have no serum marker that directly relates to primordial follicle number. As far as I know there is no product from the primordial follicle that can be measured in the serum. All of the markers we have, including ovarian ultrasound quantification of antral follicle number, are a measure of ‘ovarian response’ not a measure of ‘ovarian reserve’ as used to reflect the number of primordial follicles remaining in the ovary. That is why I find this report exciting. It sheds scientific light by bringing focus to the concept of real-time ovarian function as the outcome parameter in all studies of this nature. The authors discuss serum levels of AMH, not ‘diminished ovarian reserve’.

Clearly we have a great deal of work cut out before we can prove that cancer in young girls reduces serum AMH levels by reducing the number of primordial follicles in the ovary. From this perspective it is time for us to stop fooling ourselves into thinking that we are measuring ovarian reserve when in fact we are measuring ovarian response. I propose that we expunge the term ‘diminished ovarian reserve’ from usage as it is currently employed. Instead, let’s talk about reduced serum AMH...
levels. As a specialty we must hold investigators accountable to provide the specific data that demonstrate the specific pathophysiological mechanism of said reduced levels. Until this is demonstrated we are not able, in good scientific conscience, to call this ‘diminished ovarian reserve’.

I was also heartened that the authors refrained from employing the terms ‘premature ovarian ageing’ or ‘premature ovarian senescence’ in their report. These terms are used frequently in the literature to describe the pathophysiology in young women who have diminished markers of ovarian response, such as reduced serum AMH levels, inhibin B levels or elevated serum FSH levels. This assumes that the pathophysiology of the impaired ovarian response involves pathways that are extant in the normal ageing process, in most cases without a shred of evidence to support such a claim. Such language runs the risk of confusing scientists in other fields as well as giving patients the worry that their entire bodies are ageing prematurely. I would ask that we also expunge the use of these terms to describe evidence of an impaired ovarian response in young women unless there is clear scientific evidence presented that molecular mechanisms and pathways of the normal ageing process are involved.

I am reminded by the authors that there is a published and peer-reviewed pathway forward that is being used by the National Fragile X Foundation, an organization that represents women who have primary ovarian insufficiency related to a premutation in the FMR1 gene. This organization now refers to the condition as ‘FXPOI.’ Investigators are now using this term in their publications (Hunter, 2008). We have the opportunity to communicate clearly about the continuum of impaired ovarian response in young women. We can change how we talk about women and their ovarian function to ways that appeal to the women with the condition. Women who develop evidence of impaired ovarian response in association with amenorrhoea before the age of 40 are clearly out of the normal range with regard to the age-related decline in ovarian function. Menopause is defined as the permanent cessation of menses and results from the depletion of potentially functional primordial follicles. The mean (± SD) age at the time of normal menopause is 50 ± 4 years (van Dorp et al., 1997). As I have opined in print before, the most accurate term for the continuum of impaired ovarian response in women <40 years of age is ‘primary ovarian insufficiency,’ as first used by Fuller Albright in his 1942 publication (Albright et al., 1942; Welt, 2008; Nelson, 2009). As outlined in Table I from the New England Journal of Medicine the clinical states are ‘occult primary ovarian insufficiency’, ‘biochemical primary ovarian insufficiency’ and ‘overt primary ovarian insufficiency’. The scientific advantages of these terms are that they (i) describe a continuum of impaired ovarian response by describing the clinical state and (ii) do not ascribe a specific pathophysiological mechanism to the state, such as reduced ovarian primordial follicle number or ‘premature ageing’. This is important because we know that primary ovarian insufficiency can occur by other known specific pathophysiological mechanisms such as autoimmune lymphocytic oophoritis or mutations in the FSH receptor (Aittomäki et al., 1995; Bakalov et al., 2005). As we learn more about the specific genes that play a role in the pathophysiological mechanism we will need terminology that can (i) identify the clinical state along a continuum and (ii) be paired with each separate specific mechanism. For example, we will refer to a state of primary ovarian insufficiency due to mutation in a specific gene, which may well impair ovarian response by mechanisms other than reduced number of primordial follicles or ‘premature ovarian ageing’.

I am also reminded by the authors that as clinicians and scientists we have an obligation to communicate with patients in a manner that respects their emotional sensitivities. Of course we need to speak the truth, but we need to speak the truth with empathy. That brings me to the final reason to congratulate these brave investigators. They chose to use ‘people-first language’ (Wikipedia.org). I performed a search in PubMed using the term ‘people-first language’ and got the return ‘Quoted phrase not found quoted’. Therefore, I am unable to reference a peer-reviewed article on this topic other than Wikipedia. This is language designed to respect human dignity. The basic idea is to impose a sentence structure that names the person first and the condition second; for example, ‘people with disabilities’ rather than ‘disabled people.’ This places the emphasis that they are people first. So we have ‘a woman with diabetes’ rather than a ‘diabetic.’ I know many of my patients with primary ovarian insufficiency prefer this approach. I expect that women with primary ovarian insufficiency also thank the authors for taking this approach.

In sum, we have an opportunity to expunge ‘diminished ovarian reserve’ ‘premature ovarian ageing’, ‘premature ovarian senescence’ and ‘primary ovarian insufficiency woman’ from our scientific vocabulary as inaccurate, confusing and degrading terminology. I agree ‘Juliet, a rose by any other name would smell as sweet. However, my lovely Juliet, let’s call a spade a spade in science. We will speak the truth with love and scientific accuracy. Good night sweet princess, good night! Sleep well. Honorable clinical investigators are on your side.

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References


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Wolchover N. 2012 (http://www.huffingtonpost.com/2012/10/29/flat-earth-society-psychology_n_2038198.html).