The Bologna criteria for poor ovarian response; has the job been accomplished?

Sir,

I read with great interest the ESHRE consensus on the definition of ‘poor response’ to ovarian stimulation for in vitro fertilization by Ferraretti et al. (2011) published recently in the Human Reproduction. The authors, on behalf of the ESHRE working group on poor ovarian response (POR) definition, have presented an attempt to characterize this condition in a simplified and reproducible approach. A consensus was reached on the minimal criteria needed to define POR when at least two of the following three features must be present: (i) advanced maternal age or any other risk factor for POR; (ii) a previous POR and (iii) an abnormal ovarian reserve test (ORT).

Let me first applaud the conjoined and sincere efforts of the ESHRE working group to put together these three clinical criteria for one of the main enigmas of modern reproductive medicine. Indeed, POR as an early feature of low ovarian reserve has been complicating the treatment of significant proportion of infertile women since the early days of assisted reproductive technique (Surrey and Schoolcraft, 2000) and continues to be a major issue today. With pregnancy being intentionally delayed in modern societies, ovarian aging has become one of the most detrimental factors of pregnancy achievement and maintenance.

The variability regarding the definition of POR has recently been shown to be striking (Polyzos and Devoe, 2011). No doubt that a lack of a well-accepted, appropriate and commonly used definition for POR as an early sign of low ovarian reserve has prevented an accurate estimate of its incidence. Moreover, it has severely impaired progress in ovarian aging clinical research and may have prevented the development of evidence-based efficient and appropriate protocols or modalities of treatment for such women.

In order to reach a common and universal definition of POR, every one of the criteria selected should be simple, clearly defined and reproducible as has been the case when the revised polycystic ovary syndrome (PCOS) criteria were introduced (The Rotterdam Consensus, 2004). This approach had led to the performance of properly designed trials with good external validity and evolved into clear consensus on infertility treatment (The Thessaloniki Consensus, 2008) and regarding various women’s health aspects (The Amsterdam Consensus, 2012) related to PCOS patients.

Notably, when looking into the Bologna criteria for POR, although maternal age (≥ 40 years), previous POR (three or less than three oocytes with conventional stimulation) and abnormal ORT (antral follicle count < 5–7 or anti-Mullerian hormone < 0.5–1.1 ng/ml) were all well defined, the risk factors for POR were not (Ferraretti et al., 2011).

Although the exact mechanism or mechanisms for ovarian aging is still under investigation, several risk factors for its early development have been identified over the years. Currently they are classified into medical, lifestyle, genetic, autoimmune and idopathic factors (Younis, 2011). Moreover, while various risk factors for low ovarian reserve are well established, some are controversial and yet several others are still being revealed.

Although short menstrual cycle length, single ovary, ovarian cystectomy, chronic smoking, unexplained infertility, chemotherapy and radiotherapy are well-established risk factors (de Vos et al., 2010; Fritz and Speroff, 2011), others such as ovarian endometriomata and uterine artery embolization are still controversial. While several studies have showed that ovarian endometriotic cysts resection may be involved in ovarian aging development including early menopause (de Ziegler et al., 2010; Coccia et al., 2011), others have advocated that endometriomata per se would be responsible for the damage of normal ovarian tissue leading to the development of reduced ovarian reserve (Almog et al., 2011; Kitajima et al., 2011). A similar controversy is present in women undergoing uterine artery embolization for the treatment of uterine leiomyomata (Helenkamp et al., 2007; Tropeano et al., 2010). Likewise, the evidence for pelvic infection to be associated with POR is weak (presented in the article) and further prospective well controlled studies ought to be performed to establish this connection.

Furthermore, several novel medical risk factors of low ovarian reserve have been recently suggested including diabetes mellitus type I (Soto et al., 2009), transfusion-dependent β-thalassemia (Chang et al., 2011), and high-dose estrogen-treated tall women (Hendriks et al., 2011). Further studies are needed to substantiate all these latest findings, establish causality and identify the underlying mechanisms for the association between them and ovarian aging.

Similarly, while the family history of premature menopause, X chromosome derangements (i.e. mosaics, deletions and translocations) and fragile X mental retardation I pre-mutation are well-established genetic risk factors for low ovarian reserve development (de Vos et al., 2010; Fritz and Speroff, 2011) others are still developing. Several genetic investigation strategies and approaches have been employed in the last decade to elucidate the role of specific genes in ovarian aging development. Genetic strategies have included studying women with premature ovarian failure (Persani et al., 2010), investigating age at natural menopause (Voorhuis et al., 2010) and analyzing genetic predictors of controlled ovarian hyper-stimulation (Altmäe et al., 2011). Whilst genetic approaches have included array comparative genomic hybridization, genome-wide linkage analysis, candidate gene-association studies and genome-wide association studies (The Evian Workshop, 2011). Employing these strategies and approaches has revealed several novel candidate genes, specific loci or
chromosomal aberrations that could underlie the development of low ovarian reserve and POR.

Taken together, POR as an early sign for low ovarian reserve has numerous risk factors; several of which are well established, others are controversial and additional factors are still emerging. To establish a clear diagnosis of POR in accordance with the Bologna criteria, risk factors should be clearly defined. Although a key step has been introduced by the POR working group, the job is yet to be accomplished. Specific guidelines should be developed and pursued, in accordance with current knowledge and evidence, to direct clinicians and investigators to look for relevant risk factors to be incorporated into the diagnosis of POR. Doing that will reduce bias even more and ensure that all three criteria will be simple, clearly defined and reproducible.

Furthermore, it is not unusual for women above the age of 40 to have POR, especially infertile patients in an assisted reproduction setting. It is more important, and has valuable implications, to identify women at risk at an earlier age. Clear definition of risk factors will facilitate the diagnosis of young women with POR. Young women with an established risk factor of low ovarian reserve with an abnormal ORT may as well be classified as ‘expected POR’, in a similar manner to women over 40 years of age. This may contribute significantly to a more appropriate, tailored-approach treatment. It may, also, open new doors for the incorporation of young POR women into future targeted trials testing new strategies or modalities of treatment.

References


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Sir,

We thank Dr Younis very much for his letter. We consider that he is completely right; the risk factors for poor ovarian response (POR) at a young age are only briefly mentioned in our paper on POR definition (Ferraretti et al., 2011). Actually, the decision not to provide a detailed