Biomarkers of ovarian response: current and future applications

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With our increasing appreciation that simply maximizing oocyte yield for all patients is no longer an appropriate stimulation strategy and that age alone cannot accurately predict ovarian response, there has been an explosion in the literature regarding the utility of biomarkers to predict and individualize treatment strategies. Antral follicle count (AFC) and antimüllerian hormone (AMH) have begun to dominate the clinical scene, and although frequently pitted against each other as alternatives, both may contribute and indeed be synergistic. Their underlying technologies are continuing to develop rapidly and overcome the standardization issues that have limited their development to date. In the context of in vitro fertilization (IVF), their linear relationship with oocyte yield and thereby extremes of ovarian response has led to improved pretreatment patient counseling, individualization of stimulation strategies, increased cost effectiveness, and enhanced safety. This review highlights that although biomarkers of ovarian response started in the IVF clinic, their future extends well beyond the boundaries of assisted reproduction. The automation of AMH and its introduction into the routine repertoire of clinical biochemistry has tremendous potential. A future where primary care physicians, endocrinologists, and oncologists can rapidly assess ovarian dysfunction and the ovarian reserve more accurately than with the current standard of follicle-stimulating hormone (FSH) is an exciting possibility. For women, the ability to know the duration of their own reproductive life span will be empowering and allow them to redefine the meaning of family planning. (Fertil Steril® 2013;99:963–9. ©2013 by American Society for Reproductive Medicine.)

Key Words: Antimüllerian hormone, antral follicle count, biomarkers, OHSS, ovarian response, ovarian stimulation

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With our increasing appreciation that simply maximizing oocyte yield for all patients is no longer an appropriate stimulation strategy (1) and that age alone cannot accurately predict ovarian response, there has been an explosion in the literature regarding the utility of biomarkers to predict ovarian response and individualize treatment strategies. Although follicle-stimulating hormone (FSH) concentration and dynamic tests have served us well, their multiple deficiencies have been highlighted by the introduction of alternative, more informative markers such as antral follicle count (AFC) and antimüllerian hormone (AMH). The improved performance of these two biomarkers is largely due to their significantly stronger correlations with primordial follicle counts (2) (Fig. 1). Therefore, although elevated FSH remains informative and continues to be a defining characteristic of menopause (3), for assisted conception use its days may be limited. Similarly, when equivalent information can be achieved without dynamic testing, patient convenience will dictate a simpler route. At present, we are in a relative state of flux where the strengths and limitations of these newer markers continue to be fully elucidated. As with all new technologies, there is a spectrum of opinion regarding their usefulness, ranging from the early adopters to those who are potentially more reticent. The aim of this article is thus not to replicate the comprehensive systematic reviews of all biomarkers (4), but rather to focus on AFC and AMH, which are now beginning to dominate clinical practice, acknowledge their inherent limitations, and propose a vision for the future.

THE LACK OF STANDARDIZATION

The introduction of new technology is always accompanied by ongoing technical development and the inherent problems of changing indications for use and standards. Both AFC and AMH have suffered from these problems. For AFC, the primary issues are related to the dramatic improvements in resolution and the relative reduction in cost of the machines. These have resulted in a much larger number of

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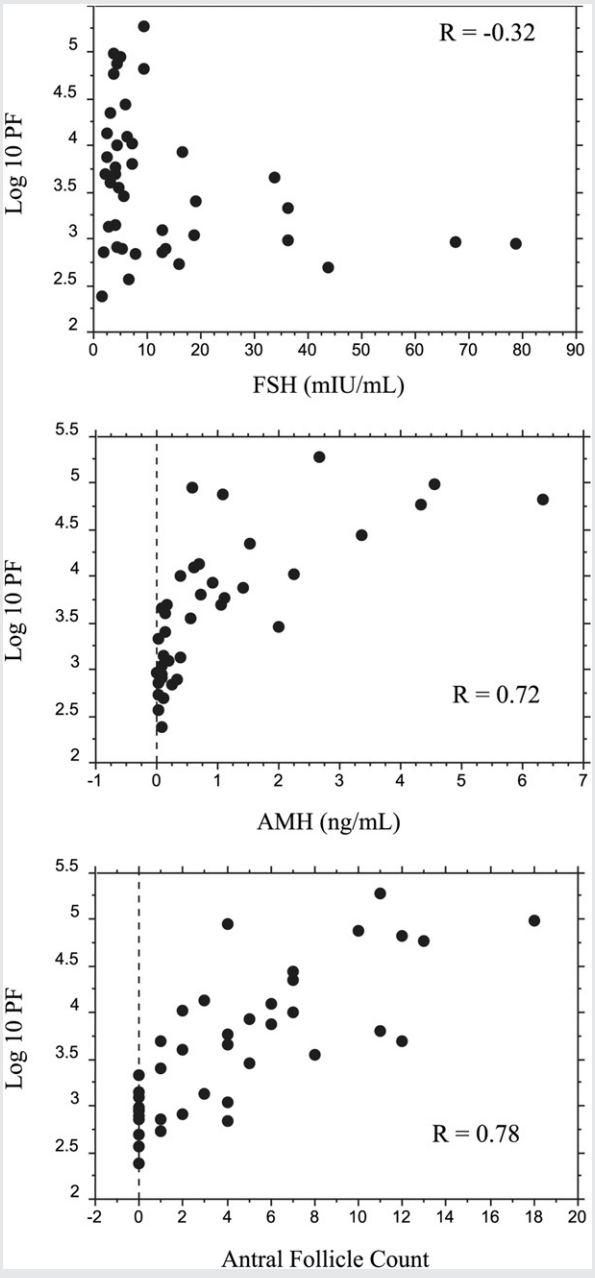
FIGURE 1



Scatter plots and correlations (Pearson correlation coefficients) for log 10 primordial follicle (PF) counts versus ovarian reserve test results. Adapted with permission from Hansen et al., 2011 (2).

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operators using a variety of machines, with a concomitant introduction of substantial interobserver variability. Just observing several operators within a single clinic will emphasize their variable scanning techniques, knowledge regarding image optimization, inclusion criteria for antral follicles (e.g., 2–5 mm or 2–10 mm), and methodology for counting and measuring follicles. Although some attempts to standardize two-dimensional techniques have been made (5), these have been limited when compared with the formal external quality control measures and accreditation that were so successful for nuchal translucency. It is therefore not surprising that recent clinical trials sponsored by pharmaceutical companies have not depended on AFC except for use as an exclusion criterion (6, 7). For example, in this context it is largely irrelevant whether there are 24 or 39 follicles, as both are currently classed as polycystic ovaries and the patient can be confidently excluded.

Accompanying this improved visualization of the ovary, the other major technical advance has been the development of three-dimensional automated follicular tracking (8, 9), which can substantially improve both intraobserver and interindividual variability (10). Although it is attractive conceptually, it is limited to one manufacturer and still requires offline analysis to ensure optimal performance, all of which have limited its widespread adoption. However, it does suggest a future that involves automated image acquisition, centralized quality control, and automated data interrogation incorporating integration of previous scan data. Collectively, this would provide health-care providers with a detailed analysis of the follicular dynamics and endometrial development.

For AMH, there have also been major technical limitations. These include the various existent forms of the assay, including the original research assays, the DSL and Immunotech assays, the Beckman Coulter Generation II assay, which combines the cross-species DSL antibodies with the Immunotech standards, the new AMH enzyme-linked immunosorbent assay (ELISA), which uses different antibodies, and the fully automated AMH assay that is due to be released by several companies (11). When the variability in the performance characteristics of these assays and the laboratories performing them, the lack of an international standards or an external quality control system, and the necessity for rapid upscaling of manufacturing capabilities are combined with the recent evidence that sample handling can dramatically alter AMH concentrations, it is not surprising that confusion and inconsistency are found in the AMH literature (12, 13). Abnormal batches of calibrators, inappropriate use of linear rather than cubic regression for standard curve interpretation, sample collection in ethylenediaminetetraacetic acid (EDTA) tubes rather than serum tubes, postage of samples before centrifuge, storage at room temperature, and poor operator reproducibility all have now been reported to be with associated increases and decreases in serum AMH levels. At present, the manufacturing issues appear to be resolved, but the importance of proper sample handling (with a dramatic ~40% increase in AMH reported at room temperature if the sample is not centrifuged immediately) remains underappreciated (13). Resolving these issues is not insurmountable, but it requires industry, researchers, and clinical pathology laboratories to provide clear guidance on their preferred assay from the point of venipuncture through to the interpretation of the results in an age- and gender-specific manner.

There are ongoing developments with respect to the measurement of AMH, which again will be subject to lack of standardization. Several groups are trying to quantify AMH within urine, which would allow it to be used as