Why we may abandon basal follicle-stimulating hormone testing: a sea change in determining ovarian reserve using antimüllerian hormone

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Antimüllerian hormone is the most informative serum marker of ovarian reserve currently available and should be considered an important part of any contemporary reproductive medicine practice. It is both more convenient and informative than basal FSH and can be assessed at any point in the cycle. It is the most useful serum method of determining ovarian reserve, which guides pretreatment counseling, choice of infertility treatment, and avoidance of ovarian hyperstimulation. The future role of basal FSH testing is in doubt. (Fertil Steril® 2013;99:1825–30. ©2013 by American Society for Reproductive Medicine.)

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From the very beginning of IVF, when multifollicular stimulation was incorporated into the approach, it was evident that patients had different ovarian responses to the same ovarian stimulation. The ability to predict this variation in ovarian response was, and still is, very useful in making ovarian stimulation both safe and effective.

This article reviews some of the history behind this effort to predict ovarian response and reviews why antimüllerian hormone (AMH) is generally a more informative and therefore a better test than basal FSH. We write as early advocates of basal FSH (J.P.T.) and AMH testing (D.B.S.).

DEVELOPMENT OF BASAL FSH AS A MARKER

When Jones and colleagues first adopted ovarian stimulation with gonadotropins into their IVF process, differential response to the same stimulation was evident in their very first series of 25 patients in 1981 (1). In their very next series, this differential ovarian response ("sensitivity," as they described it), as assessed by abdominal ultrasound, E_2 (by RIA), and cervical mucus changes, was used to adjust gonadotropin dose (2).

Muasher et al. (3), working at the Jones Institute, first reported that basal FSH levels were associated with ovarian response. This was a remarkably useful observation. The relationship between basal FSH in assisted reproductive technology (ART) outcome was studied extensively over the next decade (PubMed search on key word "basal FSH" returned 3,847 citations and on key word "day-3 FSH" returned 3,980 citations; search performed October 23, 2012) and became the gold standard for estimating ovarian reserve. J.P.T. was among those advocates who published (4, 5) and spoke on its usefulness. However, even among proponents, this test was far from perfect: it had to be done in the early follicular phase, it required concomitant E_2 determination, it

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J.P.T. is a consultant and provides expert testimony for Ferring Pharmaceuticals. D.B.S. is a scientific consultant for Ferring Pharmaceuticals; receives a royalty from a licensing agreement between University of Medicine & Dentistry of New Jersey/Massachusetts General Hospital and Beckman-Coulter for the use of antimüllerian hormone (AMH) in determining ovarian reserve; is eligible for stock options from Univfy; and is co-inventor of a method for detecting AMH in whole blood, for which Northwestern University has a patent pending.

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required a functioning hypothalamic–pituitary–gonadal system, and although an elevated FSH was a sufficiently specific marker of low response to ovarian stimulation, it was not adequately sensitive for clinical utility—only elevations carried significance. Moreover, it does not detect high ovarian reserve, a known risk factor for ovarian hyperstimulation. Because of these limitations, researchers pursued a more ideal test.

"Dynamic" or provocative tests of ovarian reserve were developed to try to make FSH more sensitive to low response: the Clomid challenge test is perhaps the best known of these (6), but others include the exogenous FSH ovarian reserve test (7) and the gonadotropin agonist stimulation test (8). These tests did in fact detect more cases of low response but involved direct ovarian stimulation and so increased cost, risk, and inconvenience.

SEARCH FOR A BETTER MARKER

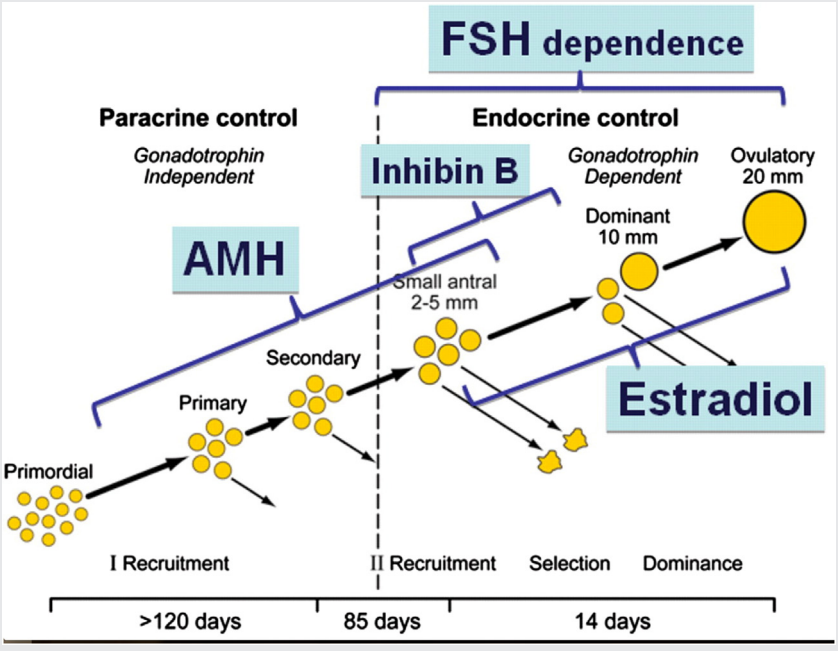
Researchers understood that many of the limitations of basal FSH as a marker stemmed from it being an indirect marker of oocyte supply. Efforts therefore focused on measuring an analyte earlier in folliculogenesis and therefore more representative of the primordial pool. The endocrine activity of the granulosa cells was targeted, because no direct secretory substances of the oocytes were known or readily available for convenient measure.

Granulosa cells were known to make many hormones and growth factors, including for example inhibins, insulin-like growth factors, activins, transforming growth factor, and vascular endothelial growth factor. Their different properties suggested some might be better indicators of ovarian reserve than others. Cell culture experiments revealed characteristic changes in the granulosa cell secretions from follicles of older women with diminished ovarian reserve (9–12). Inhibin secretion was the first growth factor that was noted to decrease with reproductive age. Thus, we (D.B.S.) began measuring it in the early follicular phase of women and noted good correlation with follicular response as a function of ovarian reserve (13–15).

However, as attractive as inhibin B seemed to be initially, its assay proved inconsistent in clinical practice owing to assay variability and lack of good precision. The variability stemmed from the use of different ELISA components and assay methodologies. Presently the assay has been improved but remains not widely used owing to a lack of clinical interest. Some of this lack of interest in the assay may be attributed to the fact that inhibin B is secreted in the FSH-dependent portion of folliculogenesis and not earlier in the process (FSH-independent portion), closer to the primordial pool. There still existed a need for a growth factor that could serve as a proxy for the size of the primordial pool that would be more informative than inhibin B.

Although AMH was first noted to be present in human follicular fluid in 1993, its function and significance were not completely understood (16). In 1999 a report using AMH knockout mice showed acceleration in the exhaustion of the primordial pool, thus suggesting a link to a growth factor that influenced rate of egg depletion (17). A 2002 report by one of us (D.B.S.) confirmed early follicular-phase serum AMH as a marker of ovarian reserve associated with number of retrieved eggs in women preparing for IVF (18).

FIGURE 1



Timing of granulosa cell secretion of AMH, inhibin B, and E_2 during folliculogenesis. Reprinted, with permission, from La Marca, et al. (54).

Toner. Ovarian reserve testing via AMH. Fertil Steril 2013.

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