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

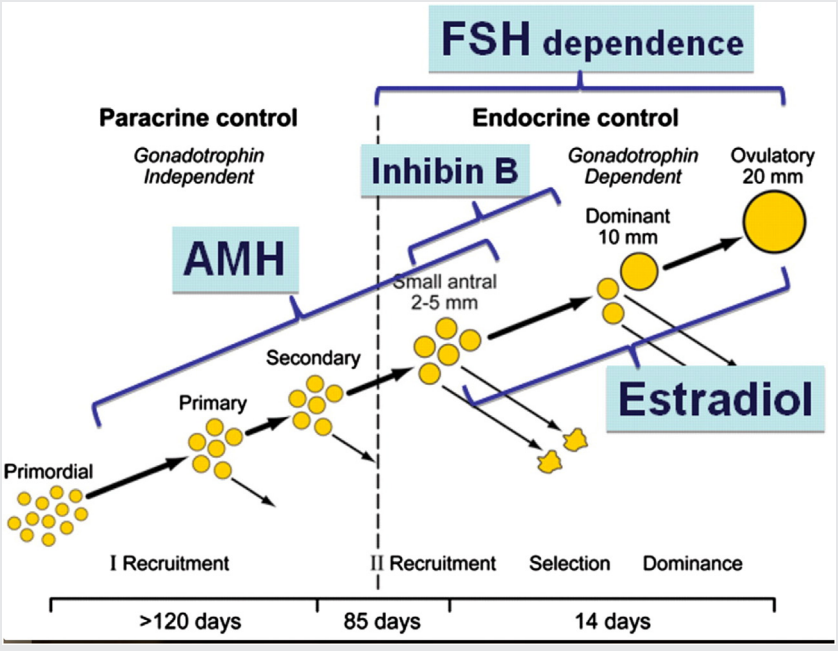
Researchers understood that many of the limitations of basal FSH as a marker stemmed from it being an indirect marker of oocyte supply. Efforts therefore focused on measuring an analyte earlier in folliculogenesis and therefore more representative of the primordial pool. The endocrine activity of the 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.

TABLE 1

Comparison of ovarian reserve markers FSH and AMH.

Feature	FSH	AMH
Site of secretion	Anterior pituitary	Granulosa of pre- and small antral follicles
Temporal change indicating ovarian aging	Latest	Earliest
Timing requirement	Cycle day 2–4 only	Any cycle day
Need for concomitant assay	E_2	None
Cycle to cycle variability	High	Low
Sensitivity for low response	Moderate	Moderate
Sensitivity for high response (risk of OHSS)	None	High
Specificity for low response	High	High
Specificity for high response	None	High
Age-specific values	Limited	Extensive information
Methodology	Automated (1 h)	ELISA (6 h)

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

AMH IS A MORE INFORMATIVE AND CONVENIENT MARKER

In the years that ensued, additional research from a variety of independent investigators throughout Europe (The Netherlands, France, Italy, Scotland, England, Germany, and Turkey) demonstrated greater clinical value of AMH. It came to be understood that as a direct secretogue of granulosa cells (at the early preantral stage) it directly correlated with egg supply.

TABLE 2

Clinical usefulness of AMH values.

AMH (ng/mL)	Clinical situation	Implications for management
Low (<0.5)	Impending onset of menopause	Counseling; consider possible options of HRT, DEXA
	Impending POF	Above, plus option for donated eggs
	Impending cancer treatment	Fertility preservation
	Test for ovarian reserve	Realistic expectations Option of aggressive OI, DHEA (49, 50), CoQ10 (51), vitamin D (52, 53)
Midrange (1.0–3.5)	Ovarian reserve testing	Guide dose selection for OI/IVF Consideration of fertility preservation if having treatment for cancer or for social reasons Provide insight into options for exclusive vs. split egg donors (i.e., the higher the AMH, the more likely to split donor)
Elevated (>3.5)	PCO or PCO-like ovaries	Consider possible option of metformin
	Increased risk for OHSS	Gentle stimulation protocols; consider GnRH agonist trigger; consideration of transferring fewer good-quality embryos (44)

Note: DEXA = dual-energy X-ray absorptiometry; HRT = hormone replacement therapy; OI = ovulation induction; PCO = polycystic ovary; POF = premature ovarian failure.

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

This can be more easily understood when referring to Figure 1, which characterizes the specific time during folliculogenesis during which AMH, inhibin B, and E_2 are produced.

Since 2002 an independent global research effort has revealed many advantages of AMH over basal FSH that have been clinically realized in infertility practice (19). These include (and are summarized in a side-by-side comparison in Table 1): [1] its relatively constant levels over the cycle (20); [2] less variation between cycles (21, 22); [3] no need for concomitant E_2 or LH measurement; [4] an earlier, more sensitive and specific marker of diminished ovarian reserve (23); [5] can predict whole range of ovarian response, from low to high (24); [6] not dependent on functioning hypothalamic-pituitary-ovarian axis—unchanged by short-term oral contraceptive pill use, first-trimester pregnancy, or hypothalamic amenorrhea (23); [7] age-specific values that have been described in a variety of sample populations (25–31); and [8] better predictor of ovarian response than FSH (24, 32, 33).

There have been two impediments to the universal adoption of AMH in this setting: assay availability and assay variability

Assay Availability

The first assays for AMH were used in research settings only. When a commercial assay became available, the one in Europe was different from the one in the United States, and neither was readily available. Despite these issues, many treatment centers in the United States have now acquired an experience with AMH and have come to rely on AMH level to guide their decisions about ovarian stimulation.

Assay Variability

The European and US assays were developed with different antibodies and reported out very different results, using different units. That problem has now been resolved by the manufacture of both ELISAs by the same company and the development of a new assay that combines the best features of both (34). Thus, currently there is only one assay.

USE OF AMH IN CURRENT CLINICAL PRACTICE

A single AMH determination is normally sufficient to estimate the oocyte supply in women presenting with infertility. Of course, no single laboratory result is always accurate, and if the AMH result is unexpected it should be repeated. However, AMH is less subject to this problem than basal FSH (35), which requires concomitant LH and E_2 measurement at a specific time of the menstrual cycle to be interpretable. Several studies examining general IVF populations have noted that low AMH cut points of 0.2–0.7 ng/mL are associated with low response: three or fewer follicles and less than or equal to two to four retrieved oocytes (36–39).

The following general guidelines in combination with the clinical history are helpful in practice approaching the initial cycle of treatment (40–44):

- Antimüllerian hormone <0.5 ng/mL predicts difficulty in IVF getting more than three follicles to grow (37–40), which in turn reduces the chance for pregnancy with IVF. Ovulation induction protocols for consideration may include those protocols designed for the most challenging patients (i.e., using microdose GnRH agonist flare).
- Antimüllerian hormone <1.0 ng/mL suggests a limited egg supply at any age. In such a case, a discussion with the patient about the short window of opportunity to conceive seems warranted (35, 40). Ovulation induction protocols may be more aggressive than one's standard approach of using GnRH agonist, for example microdose GnRH agonist flare or GnRH antagonist.
- Antimüllerian hormone >1.0 ng/mL but <3.5 ng/mL may include first-line ovulation induction protocols such as GnRH agonist or antagonist, perhaps depending on age-specific values (25–31).
- Antimüllerian hormone >3.5 ng/mL indicates an ample egg supply. Although some of these patients may also have clinical features of polycystic ovary, not all will. Either way, IVF stimulations should be mild, with a diligent effort to avoid ovarian hyperstimulation syndrome (OHSS), for example using GnRH antagonist with GnRH trigger while giving consideration to transferring fewer than the usual number of good-quality embryos (44). This clinical approach is summarized in Table 2.

Moreover, as previously mentioned, there are now useful age-specific ranges available (25–31) that provide guidance to individual women about their egg supply relative to others their age. For example, whereas an AMH level greater than the median would be reassuring, below-median levels for a specific age might encourage earlier attempts at conceiving and/or consideration of more proactive approaches and/or ovulation induction protocols to conceiving. Antimüllerian hormone values have been useful in the choice of type and amount of ovulation induction medication in anticipation of yielding an optimal egg yield while minimizing the incidence of ovarian hyperstimulation (41–43). Antimüllerian hormone is used as the primary serum ovarian reserve marker in Europe because it has been recognized to be more informative than FSH with regard to counseling for individual prognosis before treatment and choosing an appropriate ovulation induction protocol (41–43).

No marker is perfect, and AMH is no exception. There are a few caveats. Antimüllerian hormone is certainly a good predictor of egg supply, but it may not predict egg quality. At this point the question of quality remains somewhat controversial, without any real consensus. Therefore, young women with low AMH levels may have few eggs, but the eggs may be of normal quality. The primary message to consider is that their window of opportunity to conceive is likely shorter than usual, and hence they should pursue pregnancy sooner than later. Even IVF may be worthwhile if the few mature eggs obtained are proved to be of normal quality. Either way, they need to move quickly.

Older women with high AMH levels still have many eggs, but their quality is compromised because of age. In this group IVF combined with preimplantation genetic screening may assist in identifying the normal embryo among many abnormals (45).

CAVEATS

Our anecdotal experience suggests that although AMH is clearly superior to FSH in identifying high and good responders, it may be that FSH is better than AMH in discriminating the seriousness of some low-response cases when AMH <0.5 ng/mL. For instance, we have had women with immeasurably low AMH (<0.16 ng/mL) who have basal FSH levels that are acceptable (10–13 IU/L) and others with the same AMH who have perimenopausal FSH levels (>30 IU/L). The former may deserve a trial of ovarian stimulation, but not the latter (46, 47).

Turnaround time for reporting AMH results (currently 6 hours to a few days) will shorten as automated methodology becomes available. Establishment of an international standard would be beneficial, to standardize AMH assays. There are insufficient data to establish whether AMH is affected by extended oral contraceptive use of more than 6 months and pregnancy extending beyond the first trimester. However, AMH levels decline during ovulation induction (48).

It is noted that AMH levels are still increasing in children throughout adolescence until levels plateau at age 25 years, after which they begin a lifelong pattern of decline with age (30). The role of antral follicle count in relation to AMH testing deserves further scrutiny. Counting antral follicles is "operator dependent" (21) and influenced by hormonal suppression and elevated body mass index but may add further prediction to ovarian reserve assessment if performed by a consistent examiner.

In summary, AMH is now our main method of determining ovarian reserve and selecting our pretreatment counseling and choice of infertility treatment. We believe it to be the most informative serum marker available and that it should be considered an important part of any contemporary reproductive medicine practice.

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