

OVARIAN RESERVE

"Ovarian Reserve" is a term that has been in use to describe a woman's reproductive potentials since the early 1980s. Over the years, several tests have been introduced to assess the "Ovarian Reserve" (OR). These include the clomiphene challenge test (CCCT) and Gonadotropin releasing-hormone agonist (GnRHa) in 1989 and, Inhibin b in 1997, among others. Gradually, they fall out of favor and use for different reasons; great fluctuation in their estimated repeated values that make the prediction rather poor, test complexity, inconvenience and cost. This term, "Ovarian Reserve", was supposed to predict the woman's reproductive potential by assessing the number of oocytes (eggs) available at any particular menstrual cycle and the egg quality. As in the past, the presently available tests can assess the number of eggs available but they are poor predictors of egg quality! To this day the best predictor for egg quality is the woman's age.



Why does the number of available eggs matter? Women release one egg every month, and in rare occasions two. Although pregnancy can occur the first month that a couple is attempting, usually it takes more time. For the vast majority of naturally occurring pregnancies it takes six to eight months. Several factors are in play for this complicated process, but if this is a game of "natural chances" you have to play six to eight times to "win". This is translated to six to eight menstrual cycles, or six to eight available eggs. So, it appears that the more eggs are available during infertility treatment, the

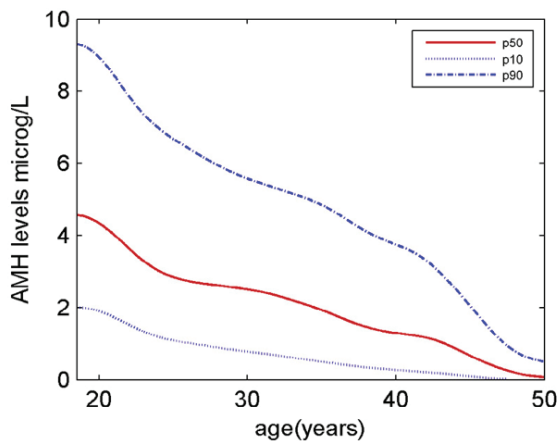
higher the chances for success, but this is an erroneous conclusion on two accounts. First, if the prediction was based just on egg numbers, women that have polycystic ovaries (PCO) shouldn't have a fertility problem! Second, clinical experience and nature had demonstrated time and again that young women with decreased number of eggs do not have difficulties in becoming pregnant.

Nonetheless, the number of eggs in the ovaries decreases progressively with age and it will be nice to know where one stands when one starts a treatment. The number of eggs help tailor the treatment for the patient. Does she need higher daily doses of medication to optimize her ovarian response, when the number of eggs is decreased, or we must decrease the daily dose to avoid severe ovarian hyperstimulation syndrome (OHSS) in cases of PCO?

The first test introduced for OR thirty years ago, and still in use, is the menstrual cycle day-3 serum level of follicle stimulating hormone (day-3 FSH). FSH is an indirect measurement of the number of eggs available. The blood levels of FSH are suppressed by the levels of circulating estrogens (E₂), which in turn depend on the number of available and developing eggs; the more eggs the lower the FSH. This test is still in use, but has serious limitations. The obtained measurements fluctuate from menstrual cycle to menstrual cycle and one measurement is not a good

predictor for poor OR. Since the level of FSH is a function of E₂, estimation of E₂ levels is useful and needed for its interpretation. Persistent elevation of FSH blood levels though will suggest poor OR. Unfortunately, this is a rather late finding in women that have poor OR. It follows that a single elevated value of FSH in a patient of advanced age (> 40 years) cannot predict failure of achieving pregnancy.

A direct measurement of the available eggs in a menstrual cycle can be performed using transvaginal ultrasound (tvU/S). This test is called Antral Follicle Count (AFC). A follicle is a small cystic structure in the ovary that holds an egg.



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The test provides (remove easily) immediate results, but requires the right equipment and ultrasonographers that have appropriate training and experience. At Delaware Valley Institute of Fertility and Genetics (DVIF&G), the ultrasonographers are

AIUM certified and use the latest models of ultrasound technology. The test is reproducible, when performed early during the menstrual cycle, and accurate under these circumstances. It includes (remove in the) counting the eggs that are senescent (atretic oocytes) and is affected by the patient body habitus, BMI > 30. Again, a decreased count of eggs is helpful in planning the treatment but not a good predictor for a pregnancy[gt1] [gt1].

Another test that was introduced in 2002, measures the blood levels of Antimullerian Hormone (AMH). This is a hormone that is produced by those eggs that are available in the ovary to be selected and developed at the current menstrual cycle. There are advantages of the AMH test when compared to the other two tests for OR. There is no fluctuation of AMH during the menstrual cycle, only in younger women with a rather large number of eggs. It does not include the senescent atretic eggs, and a decreased values appear well before the blood levels of FSH increase. Nonetheless there are limitations to this test as well. The current laboratory test is not standardized and is 4 times less precise and 10 times less sensitive than those in use in Europe and Asia.

The results of the test are affected by the use of oral contraceptives, GnRH agonist, smoking, vitamin D insufficiency and possibly obesity with a decrease in AMH blood levels while PCO has the opposite effect. There is a wide spread of the normal AMH range in younger population (see figure). It has been demonstrated in studies

performed with women in their reproductive age (from 21 to 42), accurate prediction of menopause is not feasible. By contrast, AMH can better predict menopause in an older women, from 42 to 52 years old, because of the narrower spread of its values in that group. The decreased ability of AMH to predict menopause in the general population makes it an unsuitable marker for counseling women for their reproductive life span.

A few months ago, a study comparing women with decreased levels of AMH and increased levels of FSH found no difference in the time that took them to become pregnant (within 6-12 months), as compared to those women that had better blood levels of these two hormones (see Table 1). In addition, when the values of both hormones were combined, there was not improvement of the predictive value; indicating that both hormones assess the same aspects of OR.



These findings were surprising and unexpected. It seems that AMH and FSH assess the number of oocytes that decline with age, rather than the quality of oocytes. This is why they fail to predict the chance for a pregnancy to occur. As a matter of fact, (remove since) AMH has a negative effect on the recruitment of eggs from the ovary. Therefore, a decrease in the blood levels of AMH may facilitate the recruitment of additional eggs from a progressively decreasing egg pool. At the same time, an increase in the blood levels of FSH might allow additional eggs to develop, thus increasing the chances of a pregnancy to occur. It has been established for some time now. that the chance for twins increases with advanced age.

Therefore, we might be observing a natural phenomenon of physiological compensation. While the ovarian pool of egg is decreasing, the mechanisms of egg recruitment and egg development is increasing.

	Probability for conception 6 months	
AMH	< 0.7	65 %
(ng/mL)	> 0.7	62 %
Serum FSH	> 10	63 %
(mIU/mL)	< 10	62 %

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