

## **“Ovarian Reserve” Testing**

### **What is “ovarian reserve” testing?**

This is a critical part of an infertility evaluation in which we test the reproductive potential of the eggs. A diagnosis of “diminished ovarian reserve” is made when the tests suggest that the ability of the eggs to result in a pregnancy is compromised.

### **What are the commonly performed tests for “ovarian reserve” testing?**

In many cases, a woman’s age is the single most important indicator of fertility potential. A woman’s fertility starts decreasing in her late twenties, and decreases further after age 35. After age 40, a woman’s fertility decreases very rapidly with each year. By age 45, the chance of pregnancy is very low, especially in a woman who has not conceived after 6-12 months of attempts. In fact, the chance of conceiving even with in vitro fertilization (IVF) approaches zero beyond age 45 years. This is based on the biological fact that a woman is born with all the eggs she will have. She loses eggs with each menstrual cycle. Surprisingly, this loss of eggs occurs even during pregnancy or when on birth control pills. In contrast, men produce new sperm every three months or so, and the sperm quality is much less affected by age. As we all know, a man can father a child even in old age. The most important lesson from all this is that once a woman is in a place in life where she is ready to have children, she should not delay the process. The earlier treatment is sought, the better the chance that a pregnancy can be achieved.

The commonly performed tests for “ovarian reserve” testing are the following:

- Follicle Stimulating Hormone (FSH) level. A blood test.
- Clomiphene citrate challenge test (CCCT).
- Inhibin-B level. A blood test.
- Ultrasound of the ovaries. This looks for two things: (i) the volume of the ovaries and (ii) the number of antral follicles in each ovary.
- Antimüllerian hormone (AMH) level. A blood test. This is a relatively recently developed test of ovarian reserve. It is a blood test. AMH levels do not need to be checked at any particular time of the menstrual cycle. The levels go down as a woman (and her ovaries) age, so the lower the AMH level, the lower the fertility potential.

### **What is the significance of the FSH level?**

FSH is the hormone released by the pituitary gland in the brain to stimulate the ovaries to produce a dominant follicle (which contains an egg). A “good quality” egg releases certain substances (e.g. inhibin-B, estrogen) that suppress the FSH level (negative feedback). When the egg quality is compromised, these negative feedback signals are weak and there is a resultant increase in FSH levels. An elevated FSH level therefore is an indirect indicator of compromised egg quality.

### **What is considered to be an abnormal day-3 FSH level?**

Every clinic has to determine a cut-off level that is applicable to their laboratory based on the measuring system (assay) that they use. At InVia Fertility, an FSH level less than 8 mIU/mL is considered to be normal. Pregnancy rates drop when FSH levels are greater than 10 mIU/mL and are further reduced when FSH levels are greater than 15 mIU/mL.

It is important to realize that FSH levels have low sensitivity, meaning that not everyone with a diminished ovarian reserve will have an abnormally elevated FSH level. An abnormal level does signify “diminished ovarian reserve”. However, a normal level does not signify that everything is okay. For example, a forty-five year old woman may have an FSH level of 7 mIU/mL but is NOT as fertile as a 25 year old with the same FSH level. It is important to evaluate the FSH level in the context of the full fertility evaluation.

### **What is the “intercycle variability” of FSH levels?**

When FSH levels are measured repeatedly, they can vary significantly from cycle-to-cycle. For example, a patient with an FSH level of 12 mIU/mL one month may have a normal FSH level in a subsequent cycle. Once again, this is probably because the sensitivity of a FSH level is low and the “ovarian reserve” has to be significantly compromised for the FSH levels to be persistently elevated. It is important to understand that it is the **higher** FSH level that is the best predictor of a woman’s reproductive potential.

### **Does an elevated FSH level mean that a woman will never get pregnant?**

Some women with elevated FSH levels can conceive naturally. A high FSH level simply indicates that this is less likely. Above a certain threshold, the chance of pregnancy is so low that a fertility specialist often recommends the use of donated eggs from an egg donor in order to achieve a pregnancy. Women who do beat the odds and conceive despite an elevated FSH level do have an increased risk of suffering a miscarriage.

An elevated FSH does mean that achieving a successful pregnancy with any type of fertility treatment, including with IVF, will be compromised. At the same time, a mild elevation in the FSH level may be a reason to pursue infertility treatment more aggressively and proceed directly to IVF.

Elevated FSH levels should not be used to deny a patient treatment. They are useful in counseling patients regarding their reproductive potential.

However, if the FSH levels are elevated to levels where the clinic has not seen any pregnancies, it is important that this information is used to counsel patients. In these cases, the use of donor oocytes (eggs) is a reasonable option.

### **What is the clomiphene citrate challenge test (CCCT)?**

This is like a “stress test” for the ovary. It involves having the patient take two 50 mg tablets of clomiphene citrate (also known as Clomid or Serophene) daily from days 5 to 9 of the menstrual cycle. FSH levels are measured on day 3 and –10 of the menstrual cycle. The CCCT can identify patients with “diminished ovarian reserve” that was not detected with baseline FSH measurements. Stimulated day 10 FSH levels are strongly predictive of decreased IVF success even when day 3 FSH levels are normal.

Once again, a normal CCCT does not necessarily mean that the ovarian reserve is normal. A 45 year old with a normal CCCT will not be as fertile as a 25 year old.

### **What is the significance of the ovarian volume and antral follicle count measurements?**

A normal ovary should have a volume of at least 3 cc with at least 3 – 4 antral follicles. Antral follicles are small, fluid filled cysts that are normally found in the ovaries. The higher the antral follicle count, the better the fertility potential. Small ovaries may indicate compromised fertility potential, as there may be less follicles - and therefore less eggs - available within the ovaries.

At InVia Fertility Specialists, when the baseline ultrasound at the start of an IVF cycle shows reduced ovarian volume or antral follicle counts, we generally increase the dose of the stimulation medications to achieve an optimal response. Also, if there are plenty of antral follicles the dose of stimulation medications is reduced to minimize the risk of ovarian hyperstimulation syndrome.

### **What is the antimüllerian hormone (AMH)?**

Antimüllerian hormone (AMH) also known as Müllerian Inhibiting Substance (MIS) is a new diagnostic marker of ovarian function. The existence of AMH was first proposed in 1947 by Professor Alfred Jost. This hormone is made in the testes of men. It was thought not to exist in women. In recent years, it has been found in women starting at puberty.

### **What is the role of AMH in assessing ovarian aging and ovarian reserve?**

- AMH levels decrease over time even in “fertile” women who have regular menstrual cycles.
- AMH levels correlate well with the ovarian antral follicle count and were the only levels that decreased longitudinally over time compared with FSH, estradiol, and inhibin-B levels. With ovarian aging, the first change is a decrease in AMH levels, followed by a decline in inhibin-B and finally by an increase in FSH levels.
- **AMH levels do not vary significantly during the menstrual cycle and can therefore be drawn on any day of the cycle!**
- Women who are overweight have 65% lower AMH levels than thin women, indicating that obesity may be associated with decreased ovarian reserve and/or with ovarian dysfunction.

## What are the factors that influence AMH levels?

- A. Factors that decrease MIS/AMH
  - Increasing age
  - Obesity
  - Administration of gonadotropins
  - Administration of chemotherapy or radiation
  - Surgical removal of one or both ovaries
- B. Factors that increase MIS/AMH
  - Polycystic Ovarian Syndrome
- C. Factors that do not influence MIS/AMH
  - Day of menstrual cycle
  - GnRH agonists
  - Birth Control Pills
  - Pregnancy

## What are “normal” and “abnormal” levels of AMH?

- AMH levels less than 0.2 - 0.5 ng/mL are associated with increased IVF cycle cancellation rates and fewer eggs retrieved from the ovaries.
- AMH levels greater than 2.5 ng/mL are associated with greater number of eggs retrieved and a better fertility potential.
- Recent data suggest that AMH levels may reflect fertility potential more accurately than conventional markers like FSH, inhibin-B or estradiol levels.
- AMH levels may be better indicators of the ultimate chance that a woman will achieve a pregnancy than FSH levels.
- A high AMH level (greater than 3.6 ng/mL) may predict that a woman is at increased risk for ovarian hyperstimulation syndrome. In such women, the dose of medications with IVF can be reduced to avoid this side effect of fertility treatments.

## What does all this mean?

Over the past 5 years or so, AMH has emerged as a new marker for evaluating ovarian reserve.

Potential advantages of AMH compared with other conventional markers of ovarian reserve include:

1. it is the earliest marker to change with age
2. it has the least variability from cycle to cycle
3. it has the least variability when measured on different days of the same cycle

It is important to note that no one test can predict with 100% certainty whether a woman will succeed in achieving a pregnancy. All of these tests, when taken together, allow reproductive specialists to counsel patients appropriately, and to fine tune a treatment plan that is specific to a woman's particular fertility potential. In some cases, this testing may lead a physician to use simpler treatments initially for patients expected to do well with treatment. In other cases, a physician may recommend proceeding more quickly to more aggressive treatments in order to optimize the chance of pregnancy.