HOW IS OVARIAN RESERVE ASSESSED?

The majority of indicators we have to assess OR assess egg ***quantity*** rather than egg ***quality*** and these two do not always go hand in hand.

No individual test is a perfect marker so a combination of these will be used to counsel you on the potential responsiveness of your ovary, your chances of success and help decide the best approach for your care.

1. **MATERNAL AGE**: This is one of the few indicators that can assess both quantity and quality. As discussed above egg number steadily declines from puberty and this decline accelerates from approximately 37 onwards. Similarly, egg quality declines with age predominantly as a consequence of age-dependant damage and increasing genetic abnormalities in the remaining eggs which effects the chances of successful implantation, increases miscarriage rates and also explains the increase in chromosomal abnormalities (such as Down's Syndrome) in pregnancies in mothers with increasing age. Our pregnancy calculator, available on our website, allows you to assess pregnancy rate by markers including maternal age. Alternatively, below outlines the pregnancy rates, miscarriages rates and livebirth rates by age at the Lister from 2005-2013 demonstrating the effect of age on outcome

Age at cycle	Pregnancy rate per cycle started (%)	Miscarriage rate (%)	Livebirth rate per cycle started (%)
≤ 35	55.9%	22.7%	42.7%
35 - 37	48.5%	29.9%	33.7%
38 – 39	38.5%	36.3%	24.1%
40 – 42	29.8%	45.6%	15.9%
43 – 44	15.3%	59.2%	5.9%
≥ 45	10.3%	86.7%	1.0%

2. **FOLLICLE STIMULATING HORMONE (FSH):** FSH is a hormone produced by the pituitary gland in the brain that acts on the ovary to control the recruitment, selection and stimulate the growth of follicles in the first half of the cycle in preparation for ovulation. Normally, as follicles are recruited they secrete both oestrogen and inhibin, which in turn keeps the level of FSH low. As the quantity of remaining eggs in the ovary available for recruitment decreases, the brain senses there is a low oestrogen environment and signals the pituitary to make and release more FSH hormone in an attempt to stimulate the ovaries to produce a follicle and further oestrogen.

   Two analogies can be used to help understand this process. Firstly that FSH can also be thought of as a trumpet being blown to rally the troops (eggs). The larger the number of soldiers, the more of them will hear the call and present themselves at the barracks. Once there is a response, there will be no need for further blowing of the trumpet. When the soldiers are recruited they will send a signal for the trumpeting to cease. In biology, FSH is like the trumpet - and the hormones oestradiol and inhibin are the response coming from the ovary - providing a negative feedback, suppressing the secretion of FSH and ensuring it remains low.

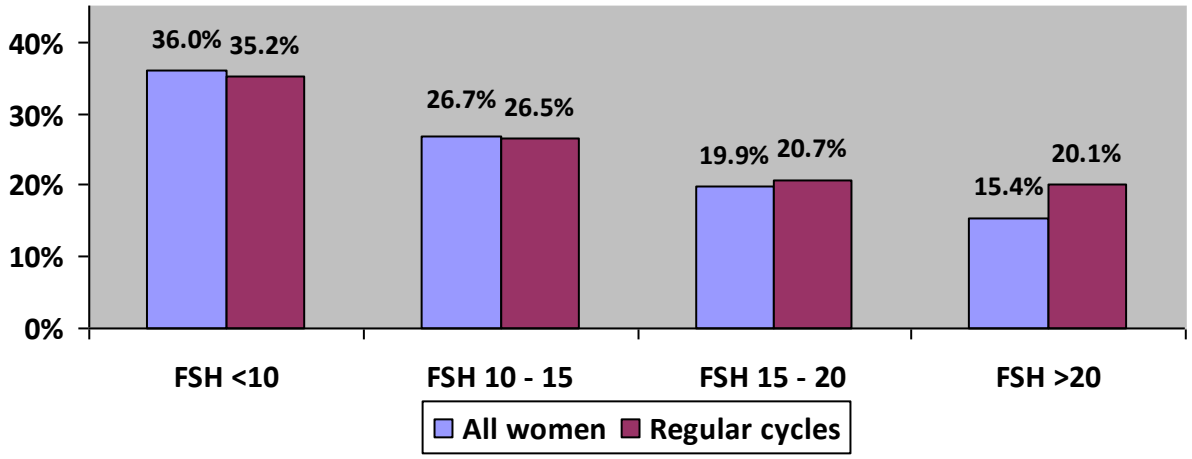
Alternatively, think of it like stepping on the gas pedal in the car to get going. The FSH is the gas, and the pituitary gland releases FSH to get a follicle "going" at the beginning of every menstrual cycle. If there are less follicles left (and perhaps lower quality follicles) the amount of "gas" has to be increased to get a follicle developing. In a menopausal woman, the gas pedal is on the floor for the rest of her life - even though there are no follicles (or eggs) left. The woman's body never gives up trying - FSH levels are permanently elevated.

FSH should always be interpreted in conjunction with an **oestradiol** result. Oestradiol should be <200pmol/l on Day 2-5, but if higher it can suppress FSH and give false reassurance.

	FSH Level (iu/l) on days 2-5 of cycle
Day 2 – 5	<10
Post -menopausal	>30

FSH is therefore low with a good ovarian reserve and elevated levels are associated with poor ovarian reserve and therefore a reduction in pregnancy ad livebirth rates in ART. This effect was demonstrated in data we published in a peer-reviewed international journal (Abdalla & Thum, 2004) and updated for 2005 – 2013 below.

Livebirth per cycle by FSH (women <40)



The reduction in outcome with increasing FSH appears to be less significant in women who continue to have regular cycles i.e. whose ovaries remain responsive to FSH and continue to ovulate.

Although, FSH is historically the most used test of ovarian reserve it has **limitations**:

- It is an indirect measure of ovarian activity i.e. measure of a brain hormone
- Considerable variability from cycle to cycle
- Considerable variability within a cycle so only interpretable between Day 2-5 of a cycle
- Because it is hormone dependant it cannot be interpreted if you are on any hormonal medication (such as the contraceptive pill)
- The ovary remains sensitive to FSH until quite late in reproductive life so it may only rise once egg number in the ovary is already very low.

3. **ANTI-MULLERIAN HORMONE (AMH)**: AMH overcomes many of these limitations as it is a hormone produced directly by the ovary. It is produced by the pool of small growing follicles (pre-antral follicles)

from which a cluster are selected, continue their growth and are seen at the beginning of a menstrual cycle (antral follicles). The higher the remaining egg number, the larger this pool is and the higher the AMH result

The **advantages** of AMH are therefore:

- It is a direct measure of ovarian function
- Less variability between cycles
- No significant variation within a cycle
- Not significantly affected by hormonal medication
- It is more accurate "snapshot" of egg quantity and slowly declines throughout reproductive life as egg numbers drop even when they remain in high numbers.

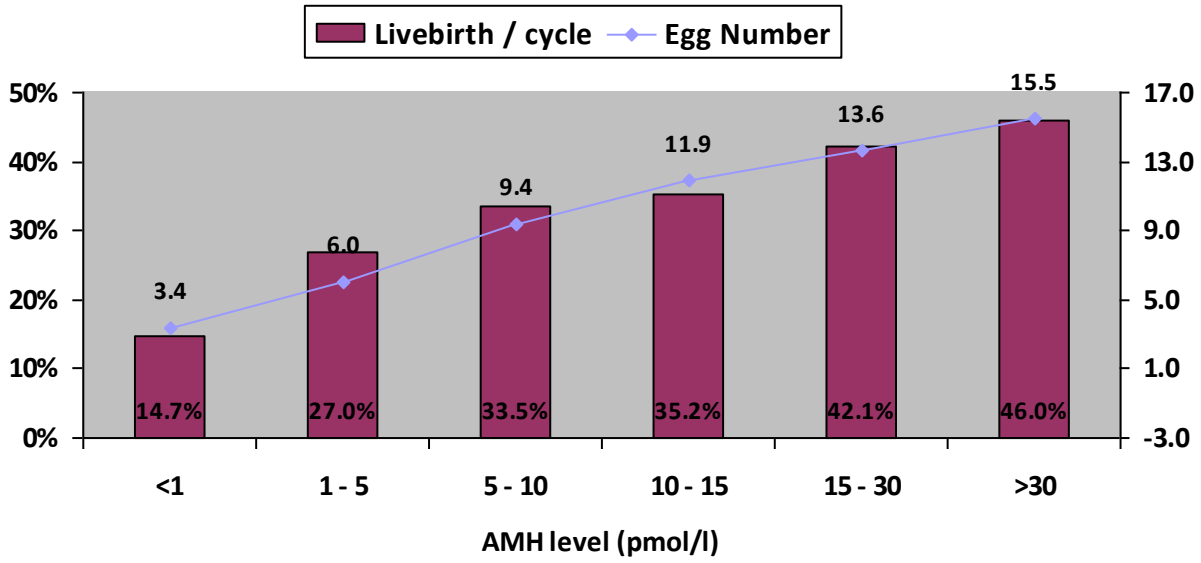
It is important to understand that AMH will naturally decline with age. Some laboratories will give "normal ranges" for AMH that do not take age into account and may therefore falsely reassure or falsely alarm. A recent study has helped us understand what is an average AMH level at various ages.

Age	Median AMH Level (pmol/l)
25	24
30	17.5
35	10
40	5
45	2.5

Adapted from Nelson et al, 2010

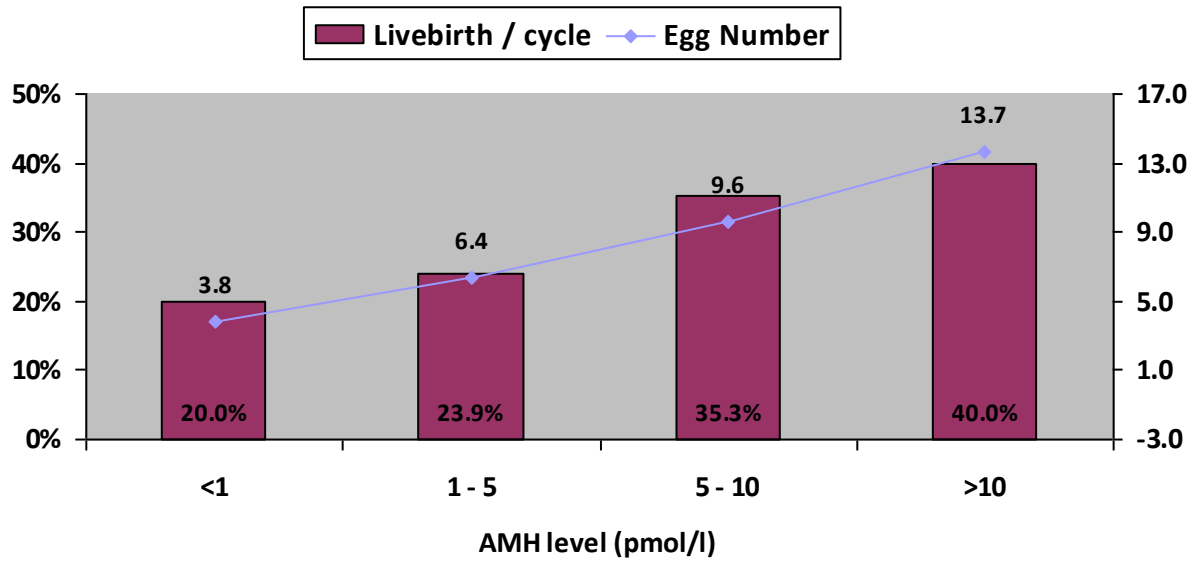
Since the introduction of AMH, we have used it as the most important predictor of ovarian reserve and our data clearly demonstrates the effect of AMH levels on the number of eggs collected and pregnancy outcome with IVF / ICSI.

Egg number and Livebirth per cycle by AMH (women under 40, 2005 – 2013)



Furthermore, even with a supposedly "normal" ovarian reserve as indicated by an FSH <10iu/l, AMH still significantly predicts response and outcome.

Egg number and Livebirth per cycle by AMH (in women under 40 with normal FSH <10)



4. **ULTRASOUND MARKERS OF THE OVARY:** Transvaginal scanning of the ovary can also provide markers off egg quanity:

    a. **OVARIAN VOLUME** decreases as egg number decreases and the ovaries may often be difficult to identify on scan after the menopause.

    b. **ANTRAL FOLLICLE COUNT (AFC):** The number of these follicles that are found in the ovary at the beginning of a cycle from which one is selected to grow and be released by ovulation is an indicator of the size of the follicle pool in general. A recent study has again helped us understand what is an average AFC for any given age.

Age	Median AFC
25	14
30	12
35	10
40	8
45	6

Adapted from Shehata et al, 2010

5. **RESPONSE TO OVARIAN STIMULATION:** Stimulating the ovary for a cycle of IVF can yield vital information on **egg quantity** (how does the ovary respond to a particular dose of stimulation?) and **egg quality** (what do the eggs and the embryos created after fertilisation look like when assessed in the laboratory?). This can often confirm what had been suggested by the other tests of ovarian reserve and more importantly can yield useful information that may alter strategies in future cycles that may improve the chances of pregnancy.

DO CHANGES IN EGG QUALITY AND QUANTITY ALWAYS GO HAND IN HAND?

Most commonly quality and quantity decline together, but even then the speed of this decline varies considerably. The average age of the menopause is 51, but at least 10% of women undergo menopause before 45 and up to 1% of women will have a "premature menopause" under the age of 40. Most commonly the cause is unknown but it can also occur after radiotherapy or chemotherapy for a malignancy, after significant surgery to the ovary or due to a genetic or immune problem.

Some of these circumstances explain when quality and quantity may not run in parallel. For example, if we look at two women undergoing ovarian stimulation for IVF treatment.

- **Woman 1**: ***33 year old*** with previous surgery to remove a large ovarian cyst who only produces ***3 eggs***
- **Woman 2**: ***43 year old*** with reassuring markers of ovarian reserve who produces ***9 eggs***

Although egg quantity is clearly impaired in the younger women (the average is 12 in women <35), the effect of her surgery where a portion of normal tissue is often also removed has not affected egg quality which is likely to be good, in keeping with her age.

In contrast, although the 43 year old has produced more (average of 6.5 in women 43-44), they are more likely to be genetically abnormal and lower quality in keeping with her age.

As a consequence, the 33 year old will still have the higher chance of achieving a successful pregnancy outcome. The table allow outlines livebirth rates at the Lister for IVF/ICSI by age and eggs collected and allows you to compare the outcome in these two scenarios.

Livebirth rates/ egg collection

No. of eggs Collected	Age at egg collection					
	Under 35	35 – 37	38 - 39	40 - 42	43 - 44	Over 45
1	7.1%	7.7%	6.8%	3.1%	2.9%	-
2	23.8%	20.7%	7.0%	10.2%	4.0%	-
3	22.2%	18.1%	15.5%	8.0%	3.0%	-
4 – 6	41.7%	29.0%	23.0%	15.4%	3.9%	1.4%
7 – 10	45.4%	37.2%	30.4%	20.4%	5.5%	2.6%
11 - 15	48.7%	40.3%	33.3%	26.2%	11.0%	5.9%
>15	50.9%	40.6%	39.7%	24.3%	14.3%	-