

Ovarian Reserve Lab Tests In IVF (Predictive value)

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Case Presentation

- ▶ 29 y/o, primary inf 1.5yr,
- ▶ Hx of irregular menses (< 20 days) but recently reg menses ,
- ▶ Hx of hypothyroidism and using levothyroxine
- ▶ Hx of I / O ×1
- ▶ BMI :27
- ▶ Hirsutism
- ▶ Galactorrhea

- ▶ Tvs : RO 26×17mm(Follicle 14) LO 24×22mm(Follicle 14mm)
- ▶ Lab tests :
- ▶ FSH :11.75/7/93
- ▶ LH : 3.7
- ▶ E2 :44
- ▶ PRL :5038.....424.....37
- ▶ TSH :1.7 TPO :292
- ▶ MRI : pituitary microadenoma
- ▶ S/A : Severe oligoasthenoteratospermia

- ▶ First ICSI (Antagonist protocol):
- ▶ 2 Gonal-f + 1 Merional for 10 days resulted in 7 F > 15mm , 3 MII oo ,3 ET, **non FHR pregnancy**
- ▶ Second ICSI (Antagonist protocol):
- ▶ TVS : Good AFC
- ▶ 2 Gonal-F + 3 Merional for 12 days resulted in 10 F > 15mm , 5 MII oo ,2 GV, 3 MI ,5 embryos, Et ...Failed
- ▶ Third ICSI (Antagonist protocol):(AMH :1.1 FSH :1.7 LH :6=4 PRL:19.1)
- ▶ TVS :RO PCO LO 25×18mm
- ▶ 1 Gonal-F + 3 Merlonal for 8 days resulted in 15 F > 15mm , 12 MII oo , 3Em,3 freezed embryos & 6 freezed oocytes

Ovarian Reserve Tests

- ▶ Such tests neither predict if a woman with regular menses is entering menopause/perimenopause nor define whether she is having a pathologic or expected decline in fertility.
- ▶ Better counseling and planning process based on which couples may choose among the available treatment
- ▶ It should be noted that ORT is not considered as sole criteria to **limit patients' access to ART or other treatments**. Moreover, according to evidence, DOR does not necessarily translate to inability to conceive.

Ovarian Reserve Tests

Disadvantage

- ▶ Further to the fact that ovarian reserve screening has not been conclusively established to reflect immediate potential for natural conception, it may potentially induce **anxiety** in women. Therefore such screening has not been strongly advocated.

Advantage

- ▶ On the other hand, some experts have argued in support of the screening general population for DOR. Some reasons to support evaluating the ovarian reserve are:
 - ▶ 1) predictive role of AMH and AFC in IVF conception chance and consequently the total fertility potential
 - ▶ 2) warning for the risk of early loss of fertility potential in low ovarian reserve if the conception is substantially delayed
 - ▶ 3) motivating patients with poor ORT to bring forward their plan for natural conception or considering oocyte vitrification

ORTs in IVF

- ▶ prediction of poor response in young women
- ▶ prediction of good response in aged women

- ▶ prediction of OHSS

- ▶ application appropriate stimulation protocols

- ▶ prediction of successful pregnancy ?????

decreased ovarian reserve(DOR)

- ▶ Include the oocyte quantity, quality and its reproductive potential.
- ▶ describes women of reproductive age with regular, mostly ovulatory
- ▶ the Bologna's criteria, by which DOR is defined by the presence of at least two of the below features :
- ▶ 1) age >40 years or other risk factor for DOR
- ▶ 2) ORT characterized by AFC less than 5-7 follicles or AMH less than 0.5-1.1 ng/mL (3.57-7.85 pmol/L)
- ▶ 3) previous poor ovarian response (less than three follicles) after a conventional stimulation protocol.
- ▶ Two episodes of poor response despite maximal stimulation can also label a patient as poor responder in the absence of advanced age or abnormal ORT.

BASAL FSH

- ▶ The baseline serum FSH measured on days 2, 3 and 4 of menstrual cycle tend to increase with advancing age.
- ▶ Major limitations in FSH measurement include significant inter- and intracycle variations and lack of consistency between assays.
- ▶ As a predictive measure, FSH possesses a high specificity (83%), while its sensitivity varies widely from 10% to 80% to identify cases with possible poor response.
- ▶ A study which employed efficiency curves has demonstrated 100% specificity for failure in achieving live birth when FSH values were exceeding 18 IU/L.
- ▶ Furthermore, the positive predictive value of FSH for poor response to ovarian stimulation or failure to conceive is higher in older women.
- ▶ Based on the extant evidence, while high FSH levels suggest a poor prognosis, **single elevated FSH value in women younger than 40 years may not predict** a reduced response to stimulation or failure to achieve pregnancy

Broekmans FJ
systematic review of tests predicting ovarian reserve
and IVF outcome. *Human Reproduction Update*.
2006

- Accuracy in the prediction of poor response and non-pregnancy is adequate only at **very high threshold levels**, but because of the very low numbers of abnormal tests **has hardly any clinical value**.
- The test will not be suitable as a diagnostic test to exclude patients, but **only as screening test** for counseling purposes

de Carvalho et al
Ovarian Reserve Assessment for Infertility
Investigation

ISRN Obstet Gynecol. 2012

- ▶ FSH continues to be an interesting test on ovarian reserve investigation, since it is an **easily accessible** and **low-cost** marker
- ▶ could be useful in pretreatment evaluation of specific groups of infertile women with **anovulatory** cycles , **endometriosis** or in patients **over 35** years of age .
- ▶ high FSH levels **should not be used to exclude** women from proceeding with ART

FSH...

- ▶ the fluctuating FSH levels should not encourage waiting for the ideal cycle, where in the FSH level is normal and IVF stimulation is prompted.
- ▶ By delaying IVF based on the FSH levels patients may need to wait for months while their age is advancing and they become closer to menopause.
- ▶ With regard to its predictive role, it has been demonstrated that elevated basal FSH levels do not correlate with aneuploidy in pregnancies.
- ▶ On the other hand, the likelihood of genetic abnormalities of embryos is augmented with advanced maternal age.

AMH

- ▶ a glycoprotein hormone of the **TGF- β superfamily** expressed by granulosa cells as soon as the primordial follicles are recruited
- ▶ The biological activity of AMH in women is not completely understood, but data along the last years suggest that it may act as a **modulator** of follicle recruitment and a **regulator** of ovarian steroidogenesis
- ▶ AMH is considered to be a marker that can estimate the **quantity** and **activity** of retrievable follicles in early stages of maturation, thus being more reliable for the prediction of ovarian response and reproductive potential

AMH...

- ▶ AMH is produced by granulosa cells of **preantral and small antral follicles**.
- ▶ The levels of this marker rise when the primordial follicles start developing. AMH release ends when these follicles reach 2 to 6 mm in diameter.
- ▶ AMH level is independent of gonadotropins, thus **remain relatively stable** within and between the menstrual cycles both in normal and infertile women.
- ▶ Low AMH levels are shown to be **linked** with (while do not necessarily predict) **poor response to ovarian stimulation, poor embryo quality, and unfavorable pregnancy outcomes in IVF.**

AMH...

- ▶ Compared to FSH, inhibin-B, and E2, AMH has the advantage of **reduced variability** of its serum concentrations along the menstrual cycle
- ▶ AMH **better marker** than age , FSH, estradiol and inhibin B.similar performance for **AMH and AFC** *Hum Rep Update 2010*
- ▶ The AFC and AMH are **the most significant** predictors of poor response *Fertility and Sterility 2010*
- ▶ but **are not predictive of non conception**, which is dependent on the woman's age.
- ▶ In clinical practice, AMH measurement may be useful in the prediction of **poor response** and also of **hyper-response**

Broekmans FJ
systematic review of tests predicting ovarian
reserve and IVF outcome. *Human Reproduction*
Update. 2006

sensitivity of 75% and specificity of 85% would imply that
test **performs only moderately**

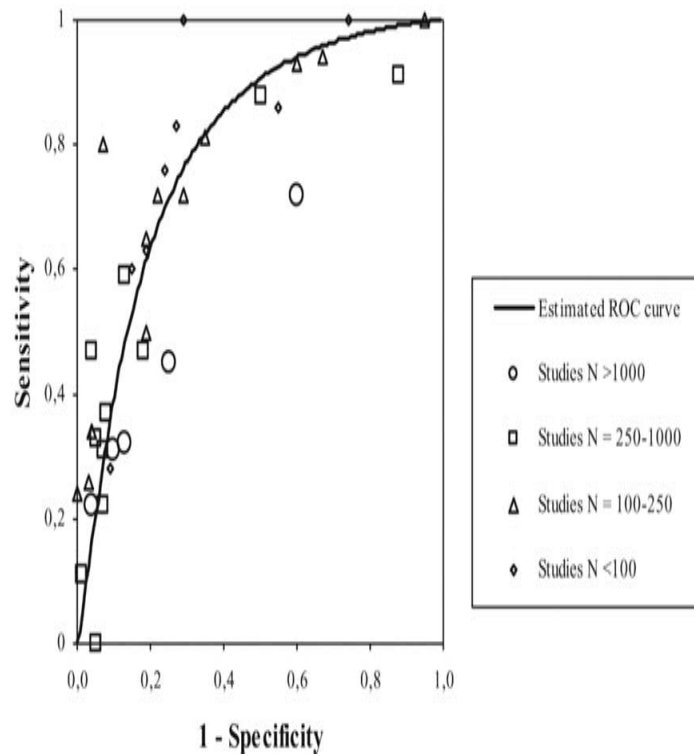
For **non-pregnancy prediction**, sensitivity of 40% and
specificity of 95% would imply that the test has **hardly any
value**, unless very low threshold levels would be used,
which will certainly lead to only very small percentages of
abnormal tests.

AMH...

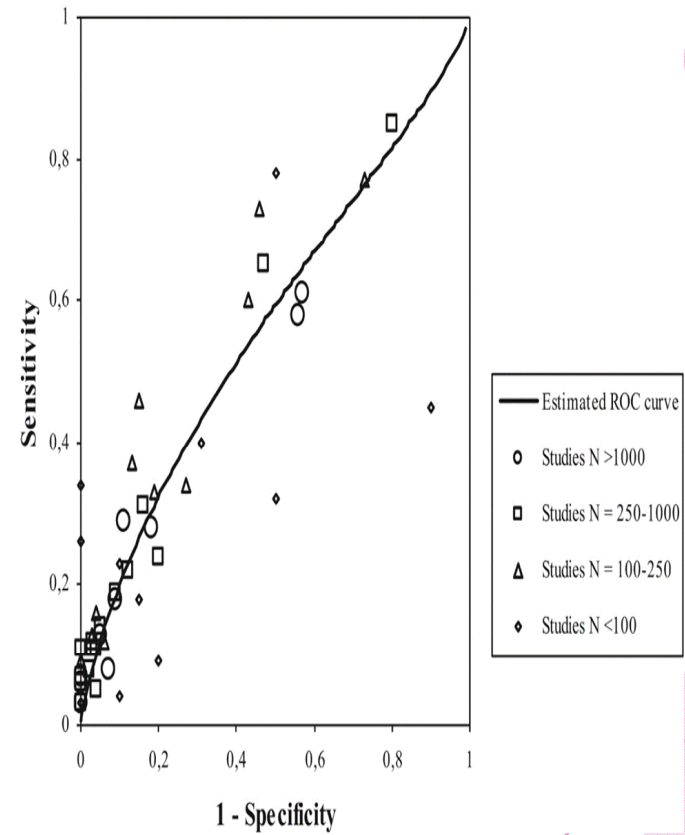
- ▶ The cut-off levels for AMH which predict poor response range from 0.5 to 1.1 ng/ mL (≤ 3.6 to 7.8 pmol/L).
- ▶ Similar to other markers, AMH levels should not exclude couples from IVF.
- ▶ In case of very poor prognosis (serum AMH < 0.1 to 0.35 ng/ mL), women should be counseled regarding the potential challenges in recruiting adequate follicles and the resultant cycle cancellation.
- ▶ AMH is considered as a proper screening test which provides useful predictive information especially in women at high risk for DOR than those at low risk.
- ▶ With regard to test validity, the AMH cutoff point of 1.25 ng/mL has yielded 85% sensitivity, 63% specificity, 41% PPV, and 96% NPV for cycle cancellation,
- ▶ **and 58% sensitivity, 75% specificity, 76% PPV, and 57% NPV for poor response.**
- ▶ Quantitative analyses have suggested that low AMH cut-off points are fairly specific for poor ovarian response to stimulation but not for pregnancy.
- ▶ Taken together, in a low-risk population, the use of AMH as a routine screening test for DOR is not warranted.

FSH

Basal FSH - Poor Response

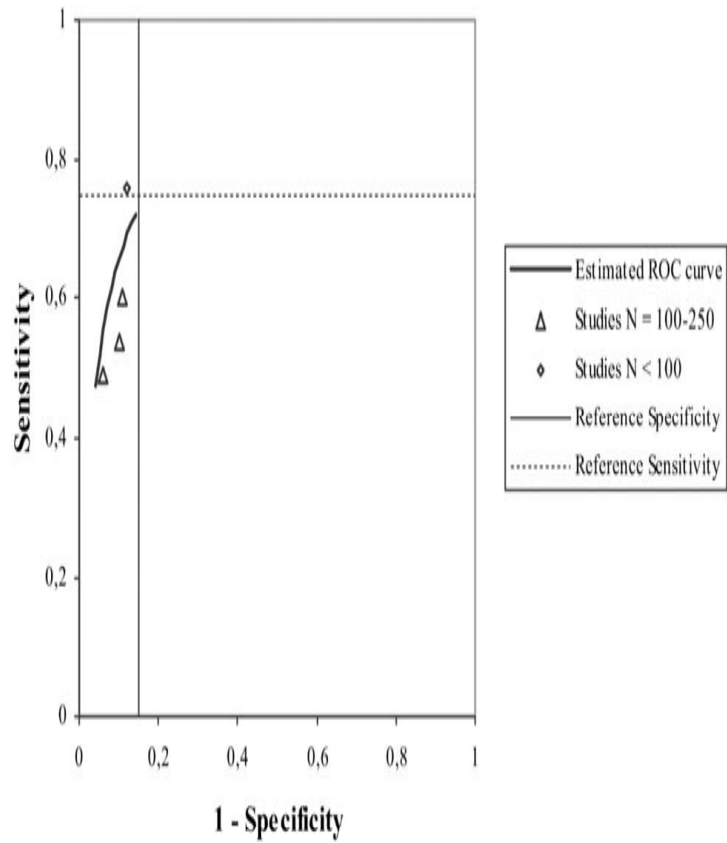


Basal FSH - Non Pregnancy

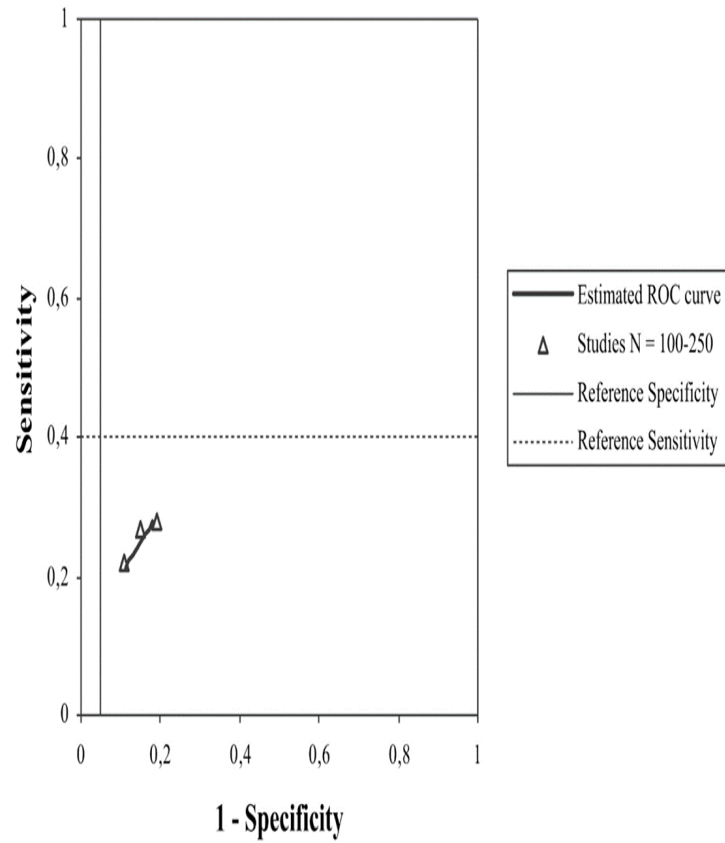


AMH

AMH - Poor Response



AMH - Non Pregnancy



Thank you for your attention



ESTRADIOL

- ▶ Basal serum estradiol level on the 2nd, 3rd and 4th day of menstrual cycle subject to a poor inter- and intracycle reliability.
- ▶ The test alone should not be employed to screen for DOR. This measure bears a value only as an auxiliary test to correct interpretation of a normal basal serum FSH level.
- ▶ An early rise in serum estradiol level suggests reproductive aging which can diminish the elevated basal FSH level into the normal range, causing misinterpretation of the test.
- ▶ There are some limited evidence favoring poor response, increased cancellation rates or lower pregnancy rates when
- ▶ the basal FSH level is normal while estradiol is elevated (>60-80 pg/mL) in the early follicular phase.

INHIBIN B

- ▶ Inhibin B is not a reliable test to predict ovarian reserve.
- ▶ The level of inhibin B may concurrently rise with GnRH or FSH stimulation, thus exhibits a high intra-cycle variability.
- ▶ Inhibin B levels also fluctuate significantly between the menstrual cycles.
- ▶ Poor responders are likely to demonstrate low Inhibin B levels (<40-45 pg/mL) as compared to women with a normal ovarian response to stimulation.
- ▶ Many studies have shown that inhibin B may not potentially discriminate between pregnancy and failure to conceive.
- ▶ Taken the above into consideration, the routine use of inhibin B as a measure of ovarian reserve has not gain evidence based support.

Dynamic tests

CLOMIPHENE CITRATE CHALLENGE TEST (CCCT)

- ▶ The CCCT includes measuring serum FSH before (cycle day 3) and after (cycle day 10) treatment with clomiphene citrate (100 mg daily, cycle days 5-9). While elevated inhibin B and estradiol levels suppress the FSH in women with responsive ovaries, the smaller follicular cohorts recruited in DOR generates less inhibin B and estradiol, resulting in subsided negative feedback inhibition of FSH secretion and higher stimulated FSH concentrations.
- ▶ Compared to the basal FSH and AFC, the CCCT does not accurately predict poor ovarian response or pregnancy after IVF.
- ▶ As a result, basal measures of FSH may be preferable over CCCT, unless the test is intentionally used to increase the sensitivity of basal FSH test.

GONADOTROPIN AGONIST STIMULATION TEST (GAST)

- ▶ This test involves evaluating the changed estradiol levels on cycle days 2 and 3 following a subcutaneous administration of a GnRH agonist. Administration of the agonist results in a massive but temporary release of gonadotropins from the pituitary. This would in turn stimulate estradiol production within a 24-hour time frame. A substantial increase or flare of estradiol in response to this stimulation reflects recruiting follicles in the early follicular phase, representing the ovarian response.

EXOGENOUS FSH OVARIAN RESERVE TEST (EFORT)

- ▶ This test is done to determine the functional condition of the ovaries. The test is based upon increased E2 and inhibin B levels 24 hours following the administration of 300 IU of recombinant FSH (r-FSH) on cycle day 3.
- ▶ Like CCCT and GAST, the methodology for EFORT lacks consistency, hence should be avoided for determination ovarian reserve.

Ultrasonographic tests

ANTRAL FOLLICLE COUNT (AFC)

- ▶ AFC is the sum of antral follicles in both ovaries, observed in transvaginal ultrasonography during the early follicular phase.
- ▶ Antral follicles are those measuring 2 to 10 mm in mean diameter in the greatest two-dimensional plane. AFC is shown to retain a proper inter-cycle and inter-observer reliability in experienced centers.
- ▶ Low AFC (ranging from 3 to 10 antral follicles) is shown to be linked to poor response to ovarian stimulation and the failure to achieve pregnancy.
- ▶ The clinical utility of AFC is limited by its low sensitivity. In addition, the inter- and intra-
- ▶ observer variability may also be limiting, particularly in centers which lack either adequate expertise or high quality ultrasound devices.

OVARIAN VOLUME

- ▶ Measuring each ovary in three plane and using the formula for the volume of an ellipsoid ($D1 \times D2 \times D3 \times 0.52$) calculate the ovarian volume.
- ▶ Ovarian volume correlates with the number of follicles and retrieved oocytes while its correlation with pregnancy is trivial.
- ▶ Moreover, patients with ovarian pathology such as PCO syndrome endometriomas, and large cysts cannot be considered.
- ▶ As compared to AFC, ovarian volume is a less preferred imaging test to screen for DOR.

OVARIAN BLOOD FLOW (OBF)

- ▶ Women presenting with highly vascularized follicles in early follicular phase are shown to have higher pregnancy rates.
- ▶ Although a recent meta-analysis evaluated the value of OBF as a predictor of IVF outcomes, the clinical value remains unclear due to the diversity of flow-derived predictors used in the literature.
- ▶ As such, OBF is neither supported as determinant measure to include infertile couples in ART nor to surmise its results.