ANTI-MÜLLERIAN HORMONE (AMH): OVARIAN RESERVE AND BEYOND

Chris White, Ph.D.
Scientific Affairs
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ANTI-MÜLLERIAN HORMONE (AMH)

Regulates sex differentiation in embryo/fetus
- Presence causes regression of Müllerian ducts in males
- Absence allows development of Müllerian ducts in females

- **Gonads**
  Develops into the ovaries in the female and the testes in a male.

- **Müllerian ducts**
  Develops into the female fallopian tubes, uterus, and upper part of the vagina.

- **Wolffian ducts**
  Develops into the male vas deferens, epididymis, and seminal vesicles.
AMH HISTORY

Alfred Jost (1916-1991)
CIRCULATING MOLECULAR FORMS OF AMH

AMH PRODUCTION IN MALES AND FEMALES

Maximal expression occurs in preantral and small antral follicles.

Sertoli cells of human testis, 3 months

AMH LEVELS IN MALES AND FEMALES

Lee. 1993 Endocr Rev.

Kelsey. 2011 Plos ONE.
CLINICAL USES OF AMH

Paediatrics *
• Differential diagnosis of intersex disorders / ambiguous genitalia
• Differential diagnosis of cryptorchidism and anorchism
• Diagnosis of precocious/delayed onset of puberty

Women’s health
Ovarian Potential
• IVF
  – Predicting ovarian response (poor / hyper)
  – Predicting reproductive outcome
  – Individualization of the treatment
• Predicting the menopause
• Cancer
Ovarian pathophysiology
• Diagnosis of polycystic ovarian syndrome
• Tumour marker in ovarian granulosa cell tumours*

*Josso. 2006 Pediatric Endocrinology Review,

Chang. 2009 Gynecologic Oncology.
OVARIAN RESERVE AND THE ROLE OF AMH


AMH COMPARED WITH OTHER MARKERS OF OVARIAN RESERVE

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
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<th>Ov. Vol</th>
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</table>

La Marca. 2010 Human Reproduction Update.
## COMMITTEE OPINION

**Committee on Gynecologic Practice**

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

<table>
<thead>
<tr>
<th>Test</th>
<th>Detail</th>
</tr>
</thead>
</table>
| FSH plus estradiol | • Serum level on cycle D2-3  
• Variation between cycles possible  
• High FSH value is associated with poor response to ovarian stimulation  
• Does not predict failure to conceive |
| AMH                | • No specific timing for the test  
• Stable value within and between menstrual cycles  
• Low AMH is associated with poor response to ovarian stimulation  
• Does not predict failure to conceive |
| AFC                | • Number of visible follicles (2-10 mm) during transvaginal ultrasound  
• Performed on cycle D 2-5  
• Number of antral follicles correlates with ovarian response to stimulation  
• Does not predict failure to conceive |
INFERTILITY STATISTICS

• Worldwide estimates (WHO) (2010):
  – One in every four couples in developing countries
  – 48.5 million infertile couples WW
  – 9% prevalence (2007 statistics)
DELAY IN WHEN WOMEN CHOOSE TO HAVE CHILDREN LEAD TO THE INCREASE IN INFERTILITY INCIDENCE

- Fecundity: ability to have viable embryo implanted
  - Decreasing quantity and quality of oocytes
- Women having first child over 30 years of age (EU)
  - ~8% in 1970
  - ~40% in 2004
- CDC: 20% of women in the US now have their first child after age 35.
2012 SART CLINICAL SUMMARY REPORT

Treatment Type
- IVF: 99%
- GIFT: 1%
- ZIFT: 1%

Procedure Frequency
- ICSI: 5%
- Unstimulated: 1%
- PGD: 67%

Diagnostic Frequency
- Tubal Factor: 17%
- Ovulatory Dysfunction: 7%
- Diminished Ovarian Reserve: 17%
- Endometriosis: 17%
- Uterine Factor: 17%
- Male Factor: 12%
- Other Factor: 12%
- Unknown Factor: 3%
- Multiple Female Factor: 8%
- Female and Male Factor: 1%
WHY MEASURE OVARIAN RESERVE IN IVF?

La Marca. 2014 Human Reprod Update.
### CUT-OFF VALUES OF AMH FOR POOR RESPONSE

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>AMH Assay</th>
<th>Cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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SENSITIVITY–SPECIFICITY POINTS FOR ALL STUDIES REPORTING ON THE PERFORMANCE FOR AMH IN THE PREDICTION OF POOR RESPONSE

Sensitivity 0.75
Specificity 0.85

La Marca. 2010 Human Reprod Update.
# Cut-Off Values of AMH for Hyper Response

<table>
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<th>Study</th>
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AUC OF BASAL AMH IS LARGER THAN THAT OF AGE AND BMI AS OHSS PREDICTOR

<table>
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<tr>
<th>Variable</th>
<th>AUC</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>BMI</td>
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<td>18.44</td>
<td>33.3</td>
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<tr>
<td>AMH (ng/mL)</td>
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<td>3.36</td>
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<tr>
<td>E2 on hCG day pg/mL</td>
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<tr>
<td>Number of follicles</td>
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ADDED VALUE OF AMH IN THE PREDICTION OF POOR RESPONSE

<table>
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<th>Prediction of poor response</th>
<th>AUC</th>
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<tbody>
<tr>
<td>Age</td>
<td>0.61</td>
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<tr>
<td>FSH</td>
<td>0.68</td>
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<tr>
<td>AFC</td>
<td>0.76</td>
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<tr>
<td>AMH</td>
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<tr>
<td>Age &amp; FSH</td>
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<tr>
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Broer. 2013 Human Reprodu Update.
COMBINING BIOMARKERS IMPROVES PREDICTION OF AN EXCESSIVE RESPONSE

<table>
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<th>Prediction of excessive response</th>
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<tr>
<td>AMH &amp; AFC</td>
<td>0.85</td>
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</tbody>
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INDIVIDUALIZED AMH-TAILORED CONTROLLED OVARIAN STIMULATION

La Marca. 2014 Human Reprod Update.
USE AMH/ AFC TO CATEGORIZE PATIENTS INTO DIFFERENT OVARIAN RESPONSE GROUPS

- **AMH 3.52-3.9 ng/mL or AFC >16 follicles**
  - Main Objective: minimize OHSS risk
  - GnRH antagonist protocol + minimal FSH stimulation

- **AMH 0.7-1.1 ng/mL or AFC < 5~7 follicles**
  - Main Objective: minimize treatment burden
  - GnRH antagonist protocol + maximal FSH stimulation

- **Low**
  - Expected poor response

- **High**
  - Expected high response

La Marca. 2014 Human Reprod Update. ESHRE consensus. 2012 Human Reproduction
AMH AND THE MENOPAUSE

• Menopausal transition marks a period of physiological change
  – Temporal changes in health and quality of life
  – Longer term changes in health outcomes
• Independent studies from a variety of sources indicate that AMH predicts the menopause *
• Stages of Reproductive Aging Workshop (STRAW) includes AMH for the first time – “it declines earlier than other signs of the menopause e.g. increasing FSH/irregular menses”

AMH AND THE MENOPAUSE

Jane

Mary

Laura

AMH (ng/ml)

Age (years)

Relative Frequency

Age at Menopause (years)

Low age-specific AMH value
Low percentile
Younger average age at menopause

High age-specific AMH value
High percentile
Older average age at menopause

Broer. 2011 JCEM.
AMH AND POLYCYSTIC OVARY SYNDROME (PCOS)

• PCOS is the most common endocrine disorder in women of reproductive age
  – Symptoms hyperandrogenism and oligo-annovulation
  – Long term associations of PCOS include; metabolic syndrome, increased risk of endometrial cancer and insulin resistant diabetes
• Women with PCOS presents with various symptoms to a range of disciplines
  – Primary care, endocrinology and gynaecology
• Debate over the diagnostic criteria
  – Transatlantic
  – 2003 Rotterdam criteria being updated

Dewailly. 2014 Hum Reprod Update.
AMH AND PCOS

Dewailly. 2014  Hum Reprod Update.
INCREASED AMH PRODUCTION BY INDIVIDUAL FOLLICLES IN PCOS

Bhide. 2015 Fertil Steril.
The use of the AMH assay as a surrogate to ultrasound is for research purpose only at the present time.

Only in-house AMH thresholds for PCOM can be used until there is standardization of the assay techniques.

AMH AND CANCER

• Established role in diagnosis and follow up of ovarian granulosa cell tumours

• Childhood cancers overall survival rates are now >90%; gonadal damage and related infertility are gaining increasing attention
  – A 10 year follow up study of childhood cancer survivors showed a decrease in AMH and the percentage of childless women in this group was higher than in an age matched cohort.

• AMH appears to facilitate establishing which chemotherapeutic agents are most toxic to ovaries

• AMH in breast cancer

Broer. 2014 Human Reproduc Update.
PREDICTOR FOR LONG TERM OVARIAN FUNCTION IN BREAST CANCER

Menopausal status and adjuvant hormonal therapy for breast cancer patients: A practical guideline


Patients with hormone sensitive breast cancer

CLEARLY PREMENOPAUSAL
- regular ovarian cyclicity prior to breast cancer diagnosis without using oral contraceptives/HRT

UNCERTAIN MENOPAUSAL STATUS
- not falling within the definition of clearly pre- or clearly postmenopausal status

CLEARLY POSTMENOPAUSAL
- older than 60 years OR bilateral ovariectomy OR amenorrhea >12 months prior to breast cancer diagnosis without using oral contraceptives/HRT

Discontinue use of oral contraceptives/HRT
START TAMOXIFEN WITHOUT OVARIAN SUPPRESSION
AND
- monitor during 2.5-3 years
  - menstrual cyclicity
  - FSH, estradiol and AMH levels

IF WITHIN 2.5-3 YEARS
- (ir)regular menstrual cycles
- one of the following:
  - FSH ≤20 IU/L
  - estradiol ≤110 pmol/L
  - AMH > 0.05 ng/mL supports a premenopausal status

5 YEARS TAMOXIFEN OVARIAN SUPPRESSION IS OPTIONAL

IF AFTER 2.5-3 YEARS
- no >1 menstrual cycle and
- FSH >20 IU/L and
- estradiol <110 pmol/L

AMH determined, should be <0.05 ng/mL

SWITCH TO AI

SWITCH THERAPY OR 5 YEARS UPFRONT AI
AMH AND MALE

• Intersex disorders / ambiguous genitalia differentiation
  – Undetectable levels indicate the absence of testicular tissue

• Puberty
  – Precocious: AMH declines
  – Delayed: persistent high levels

• EVALUATION AND TREATMENT OF CRYPTORCHIDISM: AUA GUIDELINE (2014)
  – “In boys with bilateral, nonpalpable testes who do not have congenital adrenal hyperplasia (CAH), providers should measure Müllerian Inhibiting Substance (MIS or Anti-Müllerian Hormone [AMH]) and consider additional hormone testing to evaluate for anorchia.”
OUR HERITAGE

1999  
BEC launches IOT AMH assay

2004  

2005  
BEC acquires DSL

2009  
BEC launches Gen II AMH assay

2014  
BEC launches Access AMH

Over 3000 clinical publications on Anti-Müllerian Hormone (AMH) / Müllерian Inhibiting Substance (MIS)
Fedex takes over baby delivery offering overnight express so eager mothers don't have to wait 9 months.
Thank you

xsun1@beckman.com

Moving forward with Access AMH

BECKMAN COULTER

Move healthcare forward.