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Clinical Applications of Anti-Müllerian Hormone Measurement

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DOI: 10.15428/CCTC.2019.314237

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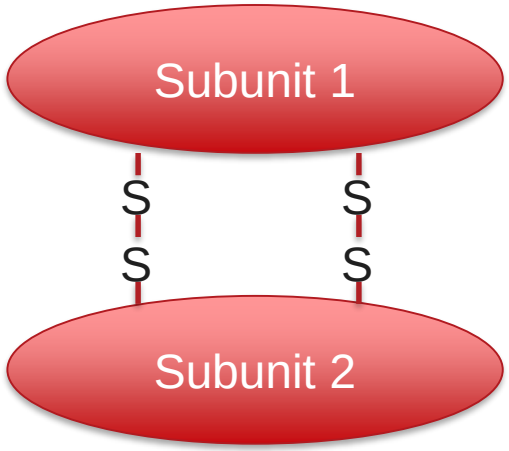
What is anti-Müllerian hormone?

- Protein hormone
- TGF-β family
- Homodimeric protein
  - Two subunits linked by disulfide bonds

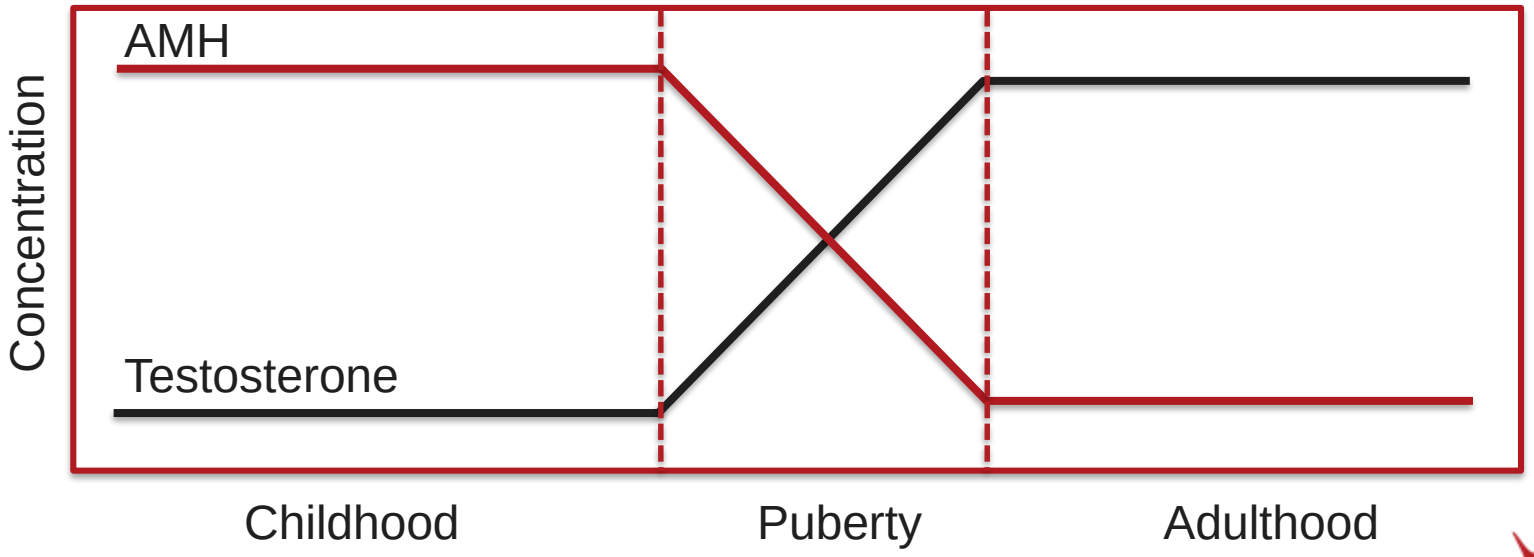


Müllerian Structures

- Derived from the Müllerian ducts
- Ducts atrophy in males during development
- Ducts persist in females
- Develop into:
  - Uterus
  - Fallopian tubes
  - Vagina

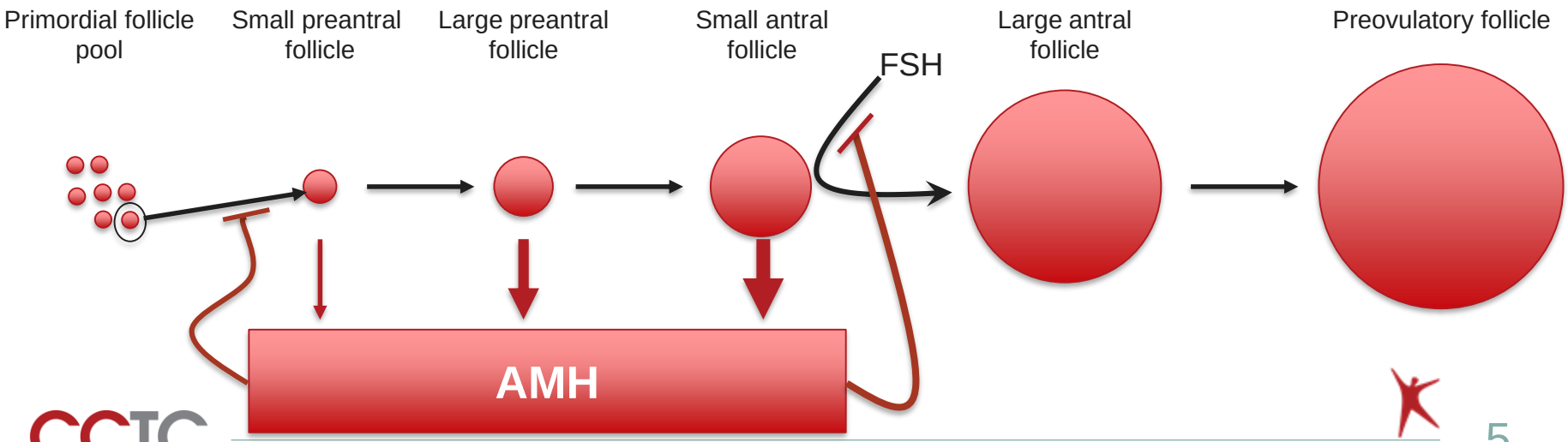
AMH Function in Males

- Sertoli cells in the testis produce high amounts of AMH
  - Suppresses formation of Müllerian structures
- AMH declines alongside rise in testosterone during puberty



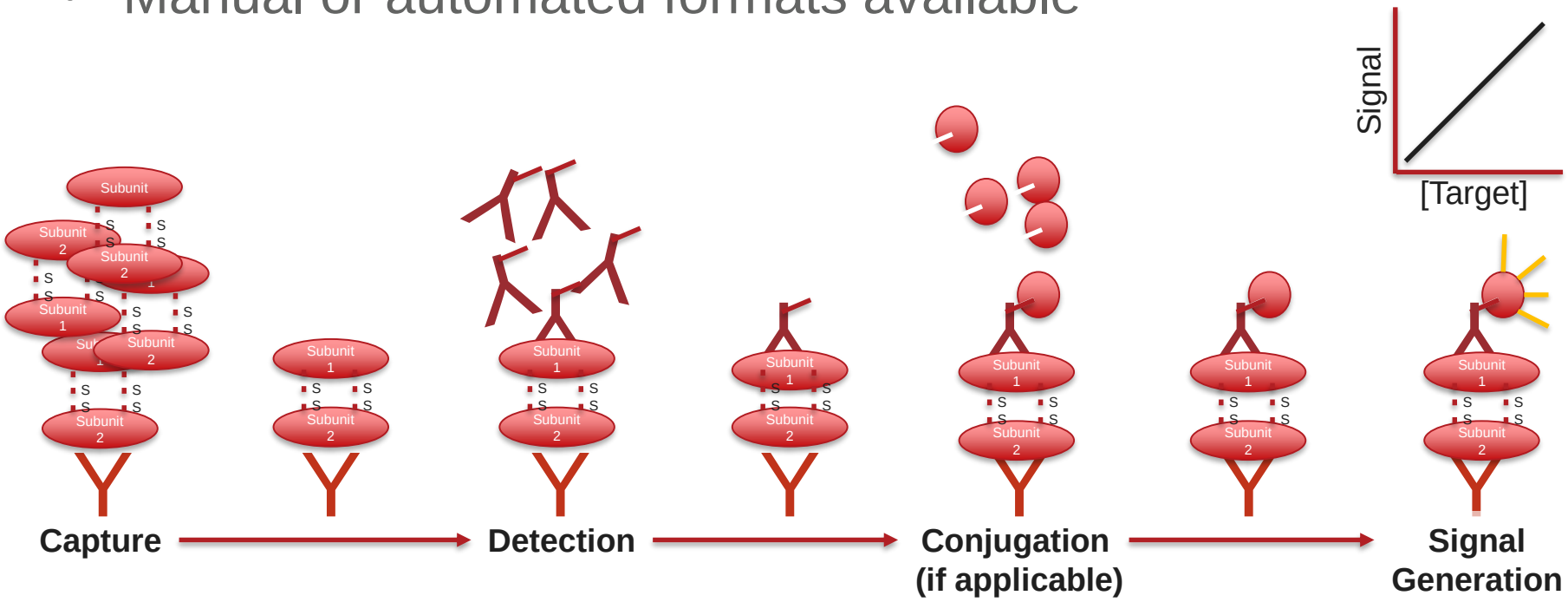
AMH Function in Females

- AMH absent during development
- Absence allows formation of Müllerian structures
- Released by preantral and small antral follicles to inhibit recruitment of additional follicles
- Preserve primordial pool



How is anti-Müllerian hormone tested?

- Anti-Müllerian hormone is measured by two-site ("sandwich") immunoassays
- Manual or automated formats available



A Brief History of AMH Testing

- Immunotech (1999) and Diagnostic Systems Laboratories (2003) developed the earliest commercial AMH assays
- Beckman purchased these companies and combined their assays in 2011
- Stability studies showed increased recovery of AMH with storage time
  - Ultimately attributed to complement interference
- Current Beckman and Roche automated methods are not affected[1]

Clinical Uses for AMH Testing[2]

- In vitro fertilization
- Assessing in-utero effects on ovary
- Impact of childhood disease
- PCOS
- Hypogonadotropic hypogonadism
- Primary ovarian insufficiency
- Ovarian surgery
- Granulosa cell tumors
- Pre- and post-cancer treatment
- Menopause
- Family planning

AMH is not a clinical measure of "fertility."

- Don't use AMH as a one-off measurement of "fertility"[3]
- Women with low serum AMH become pregnant at similar rates to women with normal to high AMH[4]
- Fecundability of women with AMH in the first quintile did not differ significantly with those in quintiles 2-4
  - Women in 5th quintile had reduced fecundability[5]
- Biomarkers of ovarian reserve do not predict fertility[6]

Polycystic Ovarian Syndrome

- Characterized by
  - Hyperandrogenism
  - Ovulatory dysfunction
  - Polycystic ovarian morphology

  } At least 2/3 = PCOS[7]
- Metabolic derangements
  - Insulin resistance
- Affects 6-12% of women of reproductive age (CDC)
- Most common cause of infertility

A role for AMH in diagnosis of PCOS?

- Polycystic ovarian morphology is currently assessed by ultrasound (antral follicle count)
  - Need to continually update cutoffs as ultrasound technology improves
  - AMH correlates well with antral follicle count[8]
  - AMH is promising as a surrogate marker for follicle count

Threshold Follicle Number per Ovary (FNPO)	Sensitivity (%)	Specificity (%)
12 (Rotterdam)	100	36
15	99	54
19	96	77
20	96	79
26	85	94

Data from reference 9

Advantages and Limitations of AMH for PCOS

Advantages

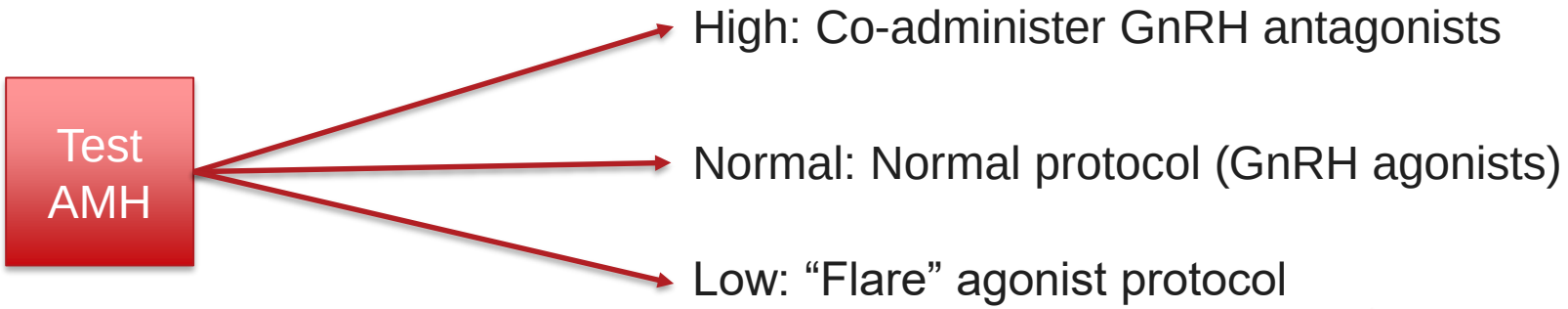
- Good correlation with antral follicle count
- Elevated in PCOS
  - Correlates with symptom severity
- Consistent throughout menstrual cycle

Limitations

- Concentrations influenced by other factors
  - Weight
  - Age
  - Smoking
  - OCP use
  - Ethnicity
- Technical challenges
  - Standardization
  - Specimen handling

AMH in Management of Infertility

- AMH is predictive of ovarian response to stimulation
- Identifies women at risk of ovarian hyperstimulation syndrome
  - Life-threatening condition
  - "Third-spacing" of fluid
- Treatment of high-risk women can mitigate much of the risk of ovarian stimulation[2]



Evaluation of Disorders of Sexual Development

- AMH is elevated in males at birth
  - Expressed solely in sertoli cells of the testis
- Can play a role in clarifying a patient's status in a disorder of sexual development
  - Must be interpreted within the context of other findings (17-OH progesterone, karyotype, etc.)
- Elevation of AMH suggests testicular tissue and can inform decision to pursue gonadectomy

AMH as a Tumor Marker

- Granulosa cell tumors account for ~2% of ovarian cancers[10]
- Traditionally inhibin B is the tumor marker of choice
- AMH is highly specific to granulosa cell tumors
- Combining AMH with inhibin B was superior to inhibin B alone for detection of recurrent disease[11]

References

1. Turner K, Larson B, Willrich MA, Bornhost J. Assessment of Complement Interference in Anti-Müllerian Hormone (AMH) Immunoassays. *AJCP* 2018; 150:S158-9.
2. Nelson SM. Biomarkers of ovarian response: current and future applications. *Fertil Steril* 2013;99:963-9.
3. Dewailly D, Laven J. Debate: AMH as the primary marker for fertility. *Eur J Endocrinol* Accepted for publication August 9, 2019.
4. Zarek SM, Mitchell EM, Sjaarda LA, Mumford SL, Silver RM, Stanford JB, et al. Is anti-Müllerian hormone associated with fecundability? Findings from the EAGeR Trial. *J Clin Endocrinol Metab* 2015;100:4215-21.
5. Hagen CP, Vestergaard S, Juul A, Skakkebaek NE, Andersson AM, Main KM, et al. Low concentration of circulating antimüllerian hormone is not predictive of reduced fecundability in young healthy women: a prospective cohort study. *Fertil Steril* 2012;98:1602-8.
6. Steiner AZ, Pritchard D, Stanczyk FZ, Ksner JS, Meadows JW, Herring AH, Baird DD. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *JAMA* 2017;318:1367-76.
7. Rottderam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41-7.
8. Fanchin R, Schonäuer LM, Righini C, Guibourdenche J, Frydman R, Taieb J. Serum anti-Müllerian hormone is more strongly related to ovarian follicular status than serum inhibin B, estradiol, FSH and LH on day 3. *Hum Reprod* 2003;18:323-7.
9. Lujan ME, Jarrett BY, Brooks ED, Reines JK, Peppin AK, Muhn N, et al. Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume. *Hum Reprod* 2013;28:1361-8.
10. National Institutes of Health. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/8642/granulosa-cell-tumor-of-the-ovary (Accessed October 2019)
11. Färkkilä A, Koskela S, Bryk S, Alfthan H, Bützow R, Leminen A, et al. The clinical utility of serum anti-Müllerian hormone in the follow-up of ovarian adult-type granulosa cell tumors--A comparative study with inhibin B. *Int J Cancer* 2015; 137:1661-71.

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
- **Consultant or Advisory Role:** No disclosures
- **Stock Ownership:** No disclosures
- **Honoraria:** No disclosures
- **Research Funding:** No disclosures
- **Expert Testimony:** No disclosures
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