

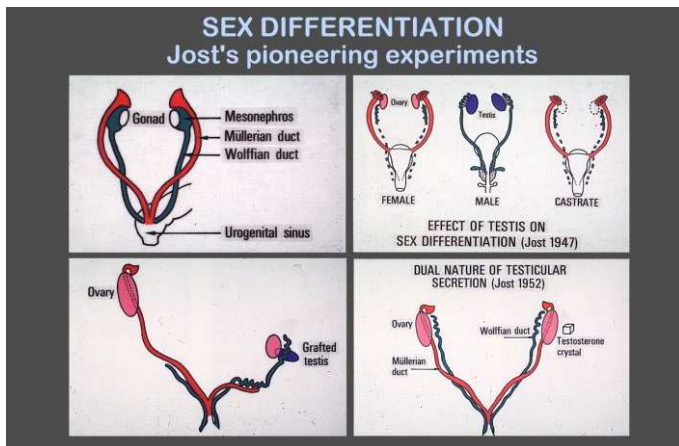
## **AMH: dernières avancées dans la physiopathologie**

**Nathalie di Clemente**

Equipe Lipodystrophies, adaptations métaboliques et hormonales, et vieillissement  
Centre de Recherche Saint Antoine  
INSERM - UMR S 938

# Anti-Müllerian hormone (AMH) Müllerian Inhibiting Substance (MIS)

Jost, 1947  
Jost, 1953

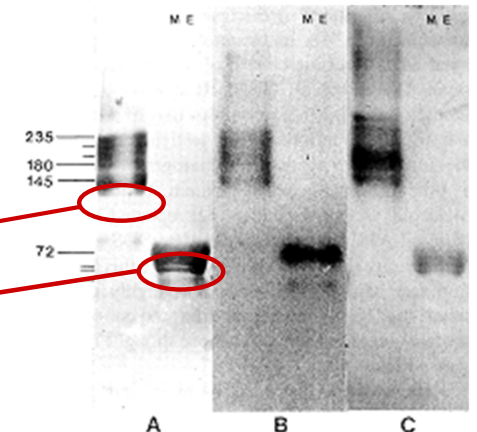


Vigier et al, 1984  
AMH expression  
by granulosa cells

Picard &  
Josso, 1984

140 kD

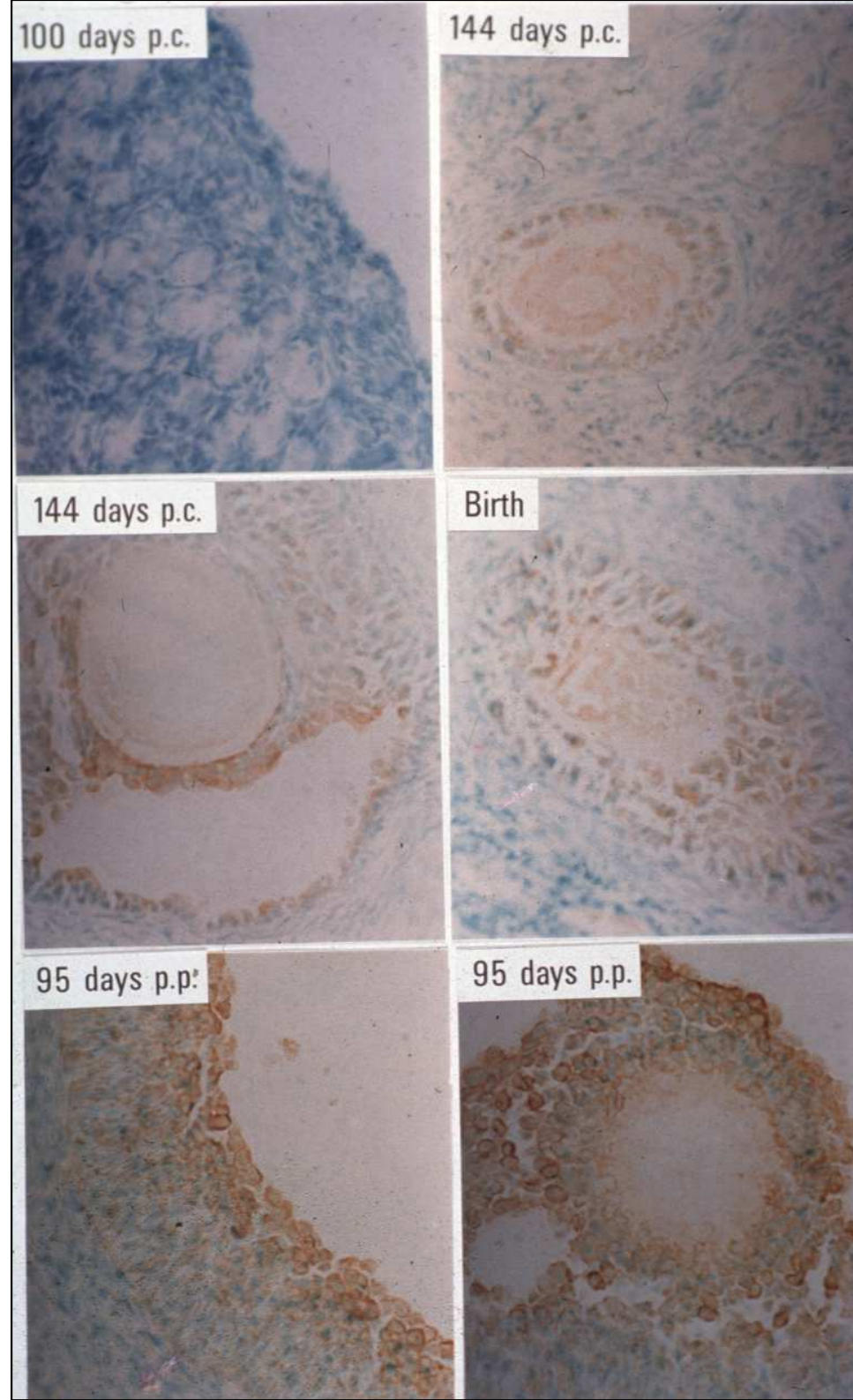
70 kD



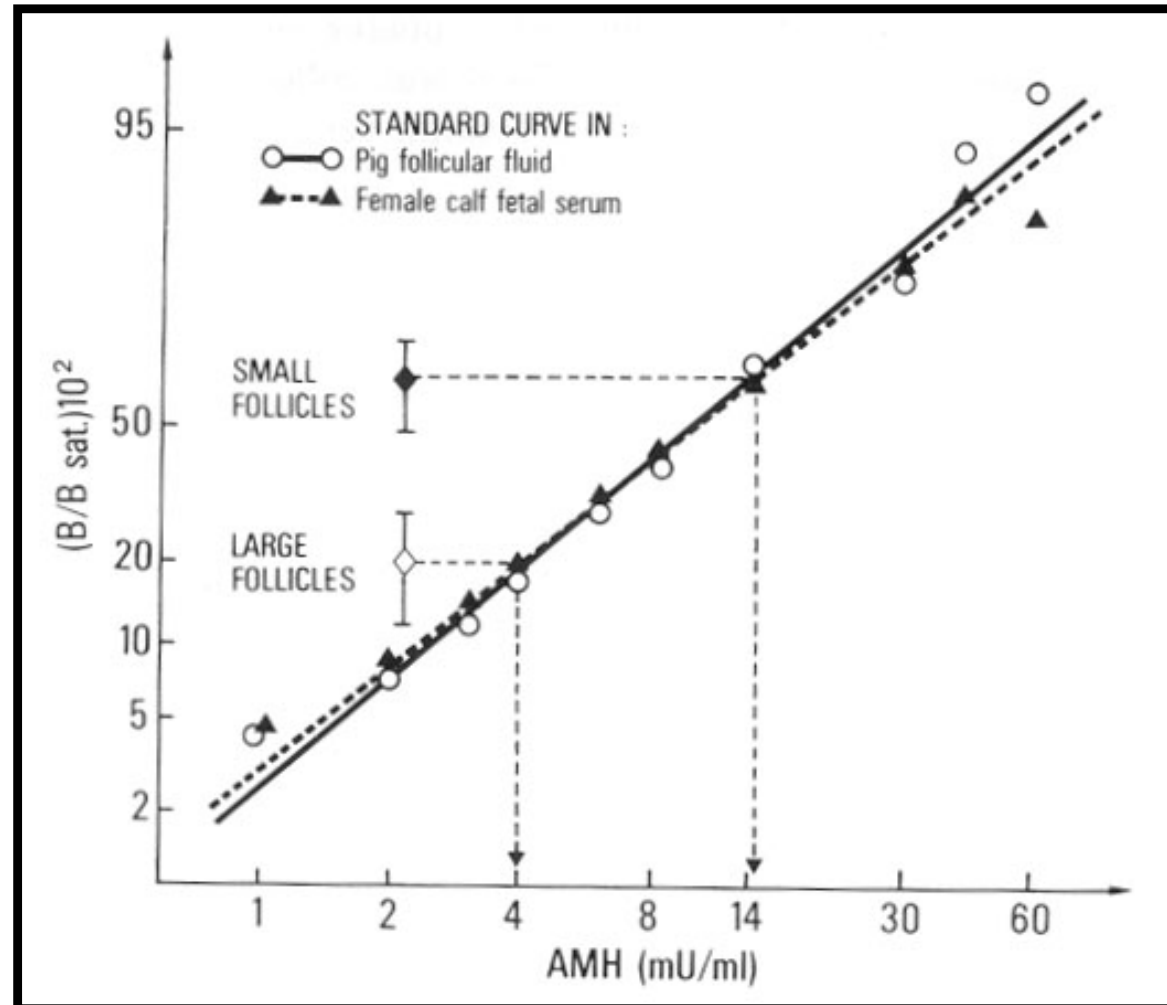
Purification of AMH

# Expression of AMH in the bovine ovary

*Bezard et al., 1987*

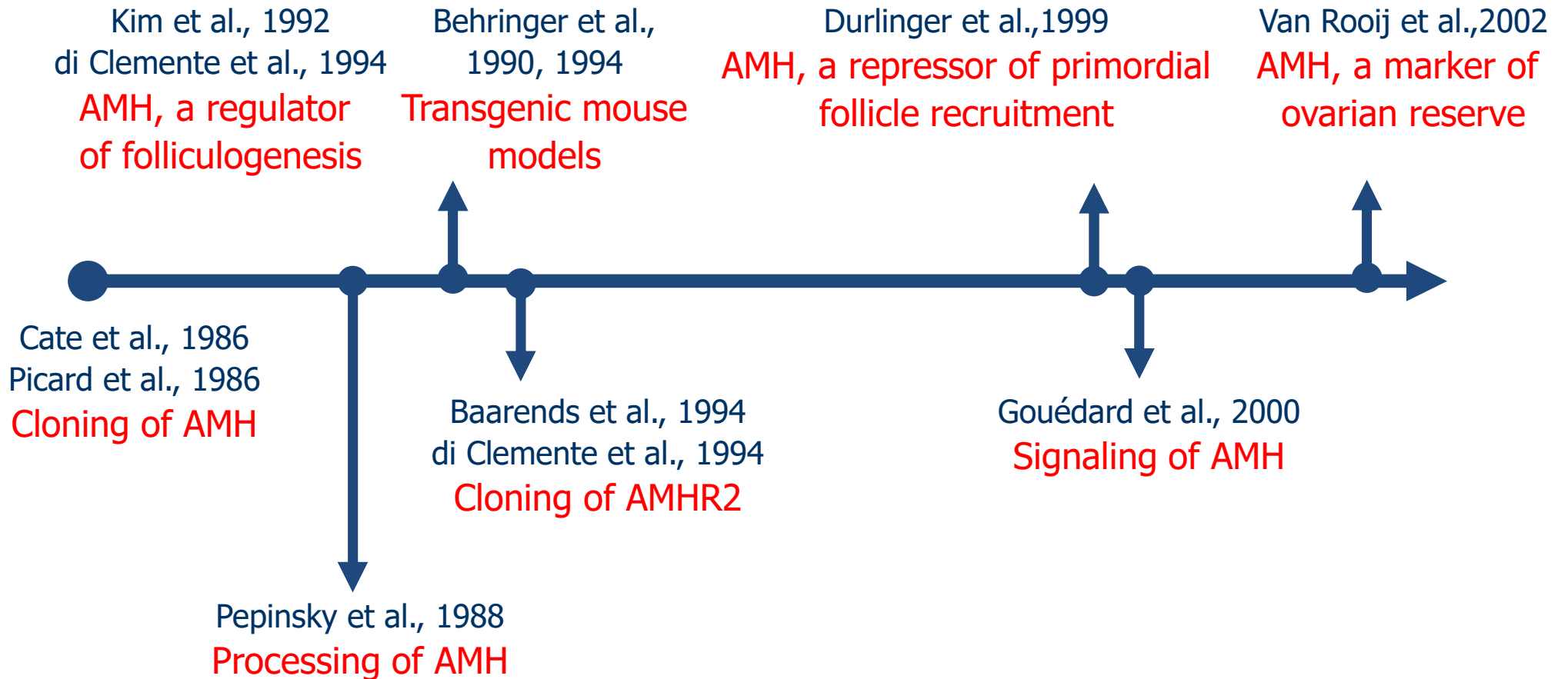


# Intrafollicular concentration of AMH in bovines

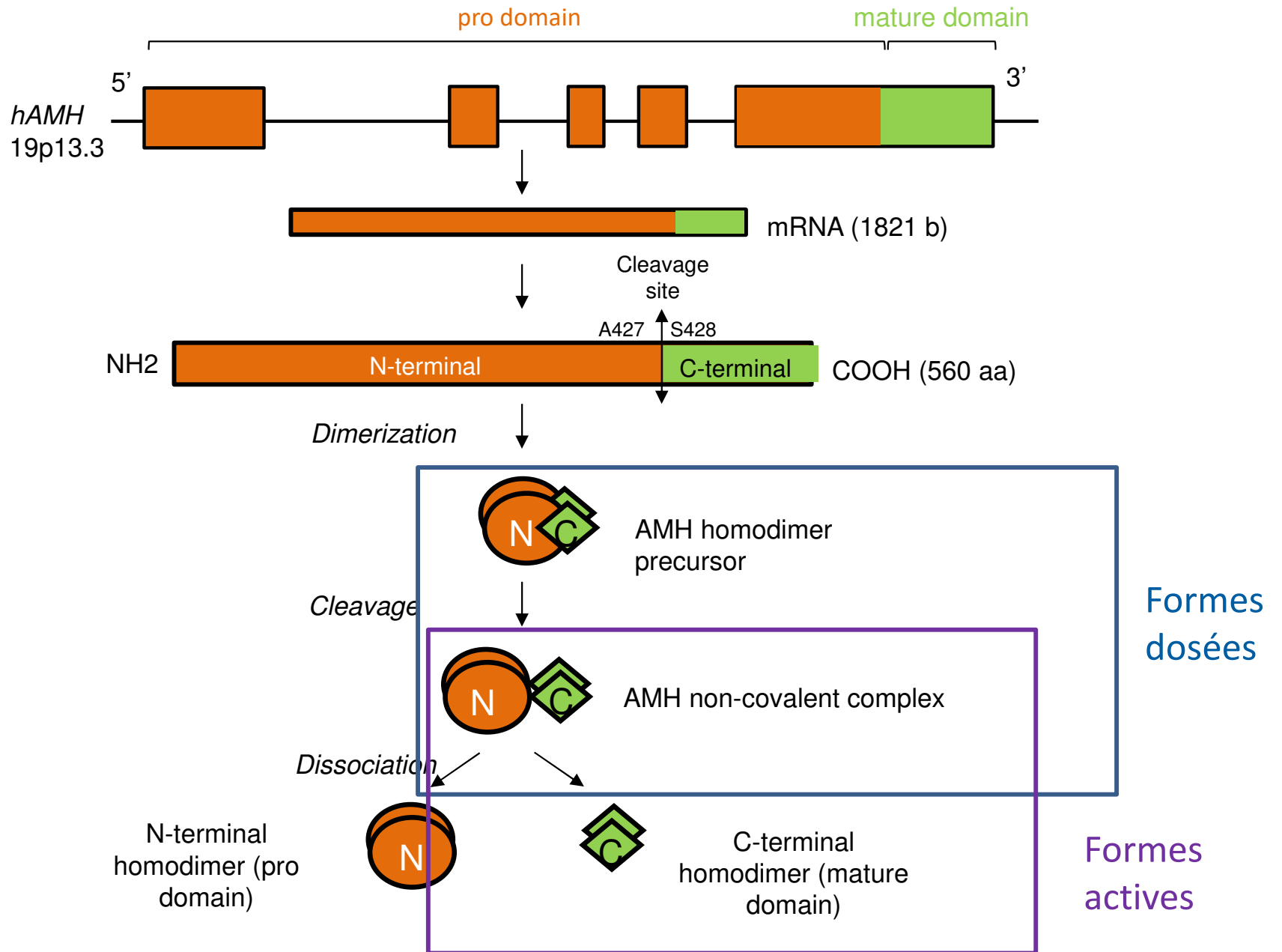


*Vigier et al., 1984*

# Anti-Müllerian hormone (AMH) Müllerian Inhibiting Substance (MIS)

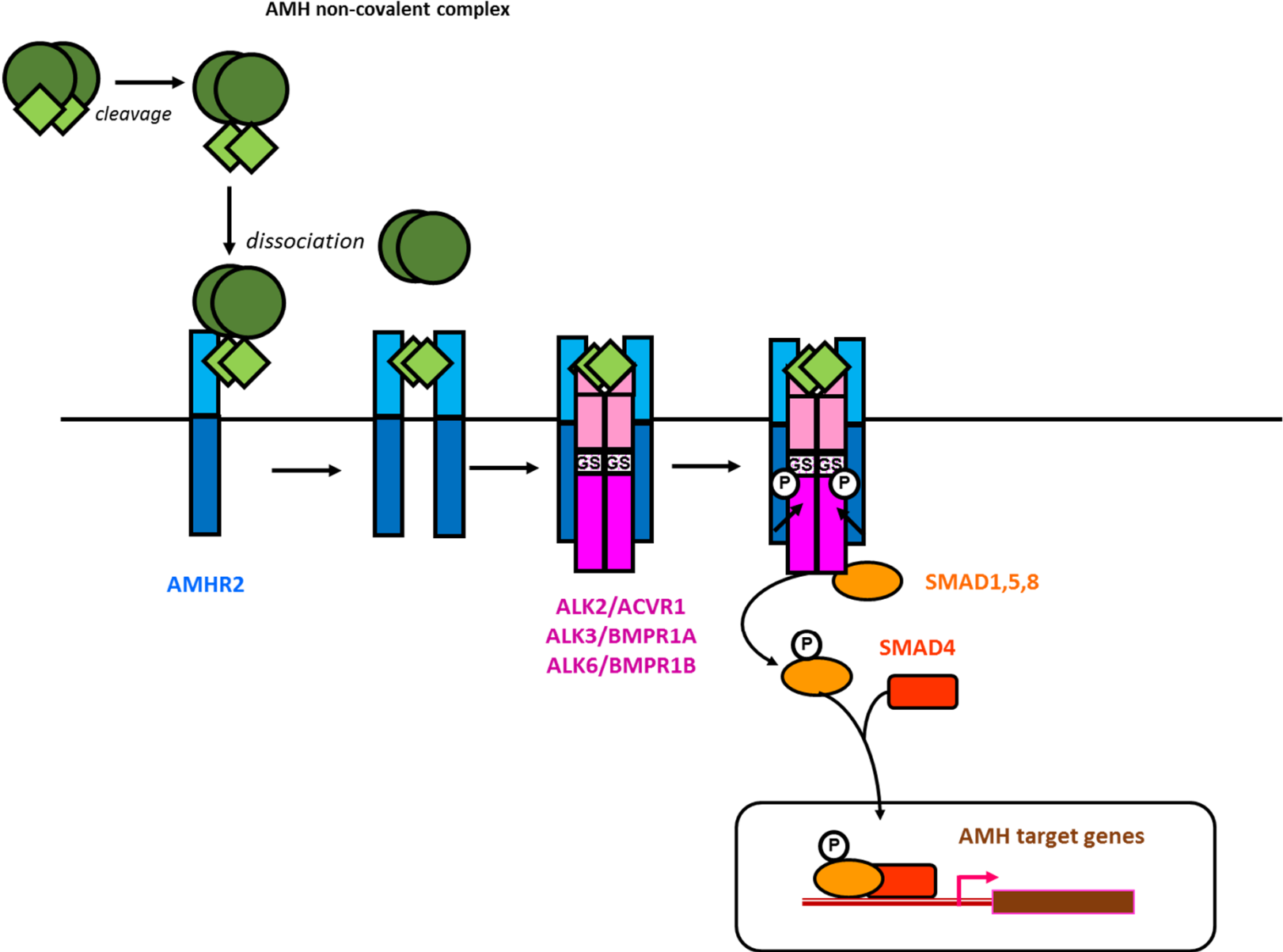


# AMH processing



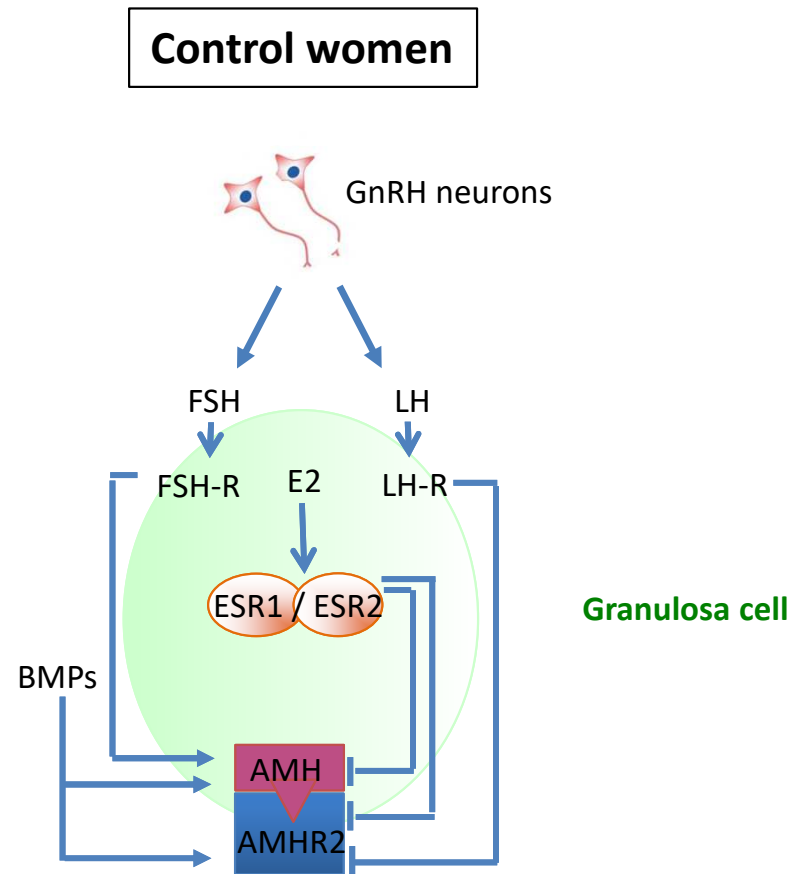
*Reviewed in di Clemente et al., 2021*

# AMH signaling



*Reviewed in di Clemente et al., 2021*

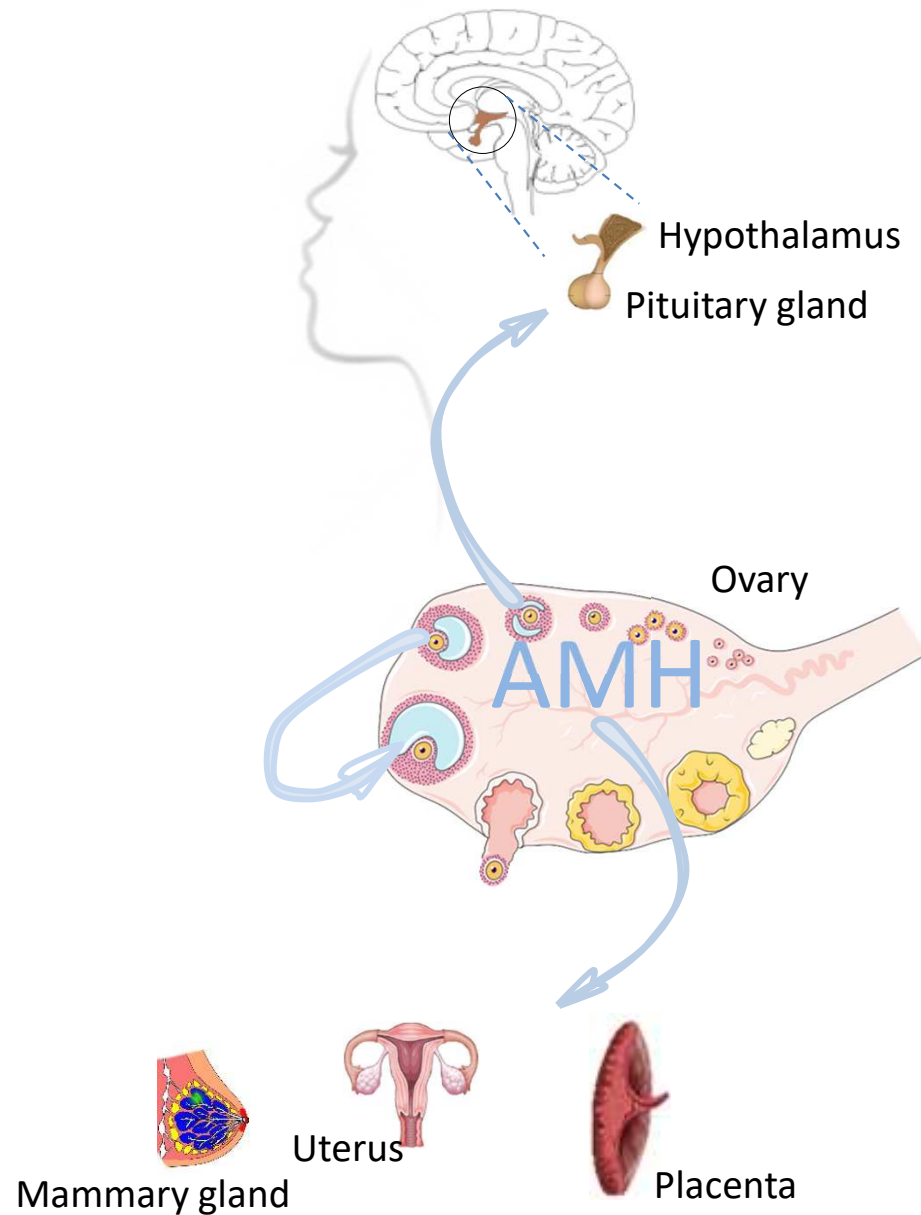
# Regulation of AMH/AMHR2 secretion



*Reviewed in di Clemente et al., 2021*

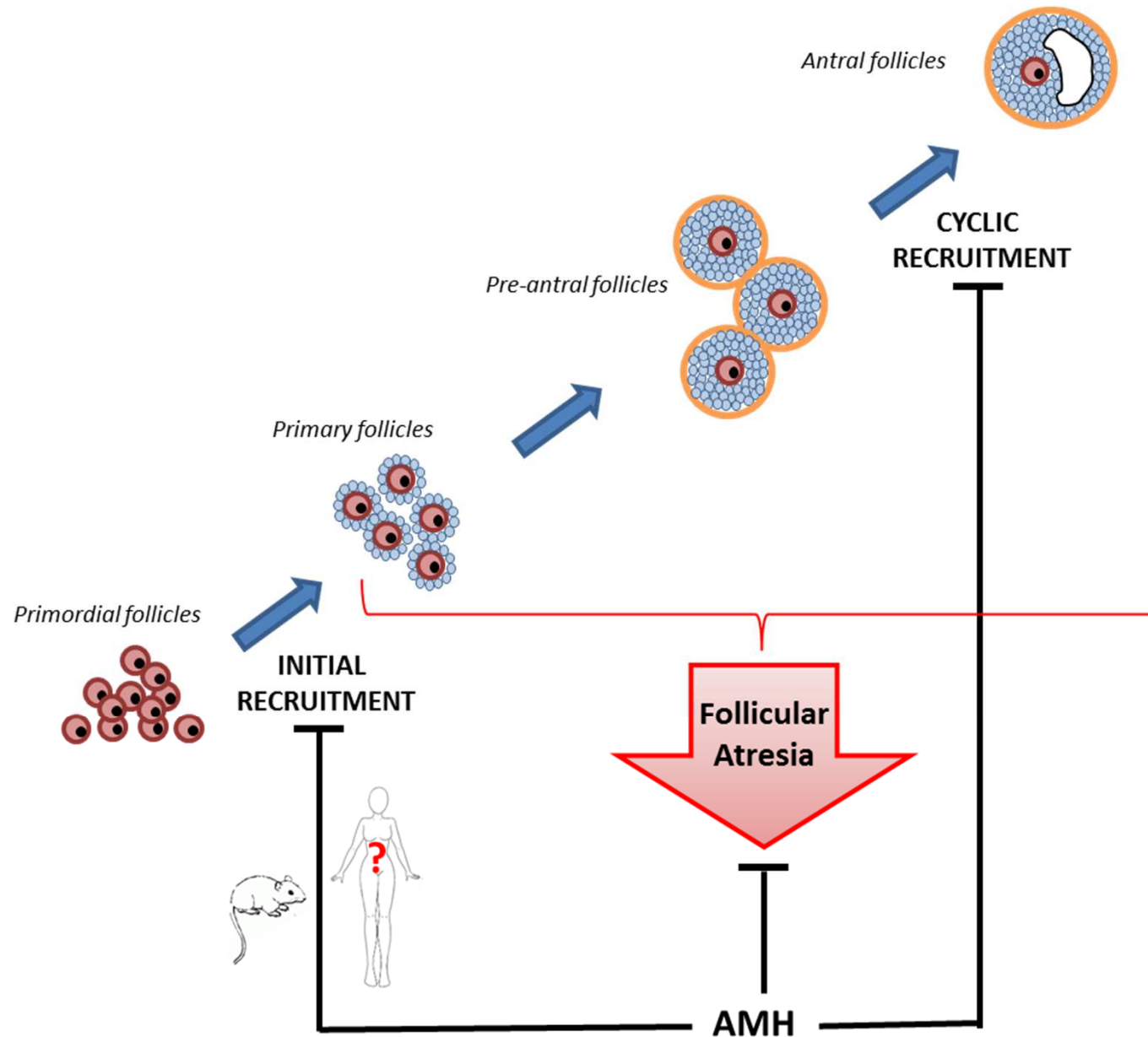


# AMH effects in females



*Reviewed in di Clemente et al., 2021*

# AMH effects in the ovaries



*Reviewed in di Clemente et al., 2021*

## AMH: a usefull marker in gynecology

- Low intra and inter variations of AMH levels during the menstrual cycle
- Numerous ELISA, both manual and automatic
- But no standard

Reviewed in:

*Moolhuijsen and Visser, 2020*

*Cedars 2022*

## AMH: a usefull marker in gynecology

- Marker of ovarian reserve
- Marker of ovarian responsiveness to COS
- Not a marker of pregnancy
- Not a marker of the age of menopause
- Marker of granulosa cell cancer, POI, PCOS

Reviewed in:

*Moolhuijsen and Visser, 2020*

*Cedars 2022*

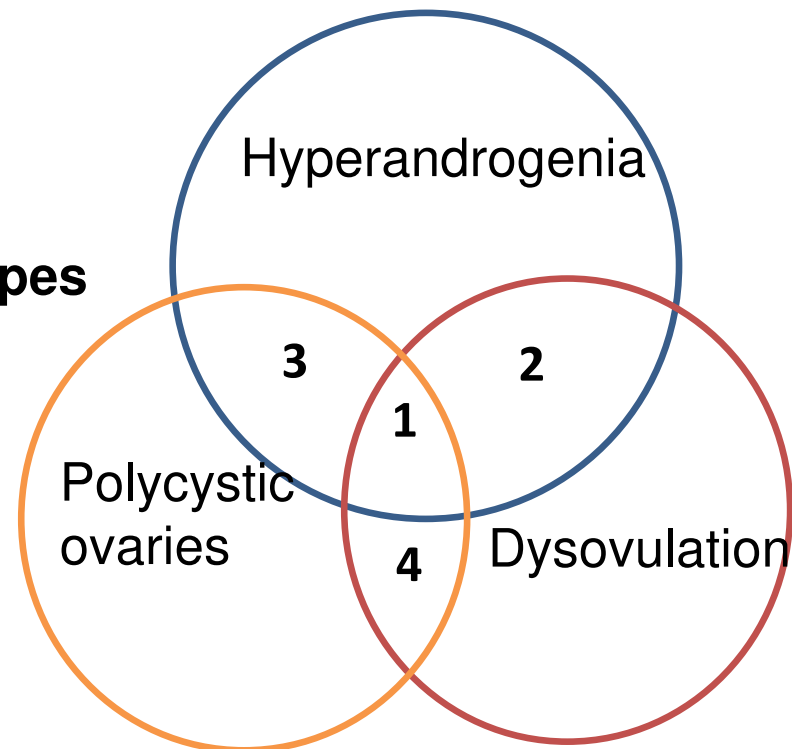
# Polycystic ovary syndrome (PCOS)

## Diagnostic criteria : Rotterdam consensus

(*Fauser et al, Fertil. Steril.*; 2012; *Teede et al, Hum Reprod*, 2018)

- ✓ Anovulation or dysovulation
- ✓ Hyperandrogenia: clinical and/or biological
- ✓ Polycystic ovaries at ultrasonography

## 4 Phenotypes



# Polycystic ovary syndrome (PCOS)

## Reproduction

- Rotterdam criteria
- High LH levels
- High AMH levels
- Pregnancy disturbances

## Metabolism

- Obesity (20-80%)
- Insulinoreistance (70 %)
- Type 2 diabetes (7%)
- Dyslipidemia (70%)
- Hypertension
- Hepatic steatosis
- Cardiovascular risks

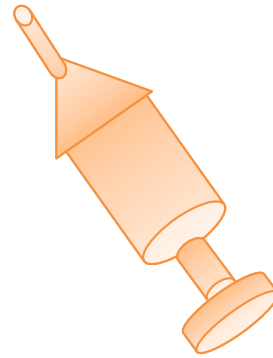
## Psychology

- Depression
- Anxiety

**AMH levels are related to the severity of the syndrome:**

- Why AMH levels are high ?
- Is AMH involved in the pathophysiology of the PCOS ?

# Regulation of AMH/AMHR2 expression in human luteal granulosa cells



Oocyte

Follicular fluid

Percoll gradient

Mural granulosa cells



Gonadotropins

ELISA

AMH secretion

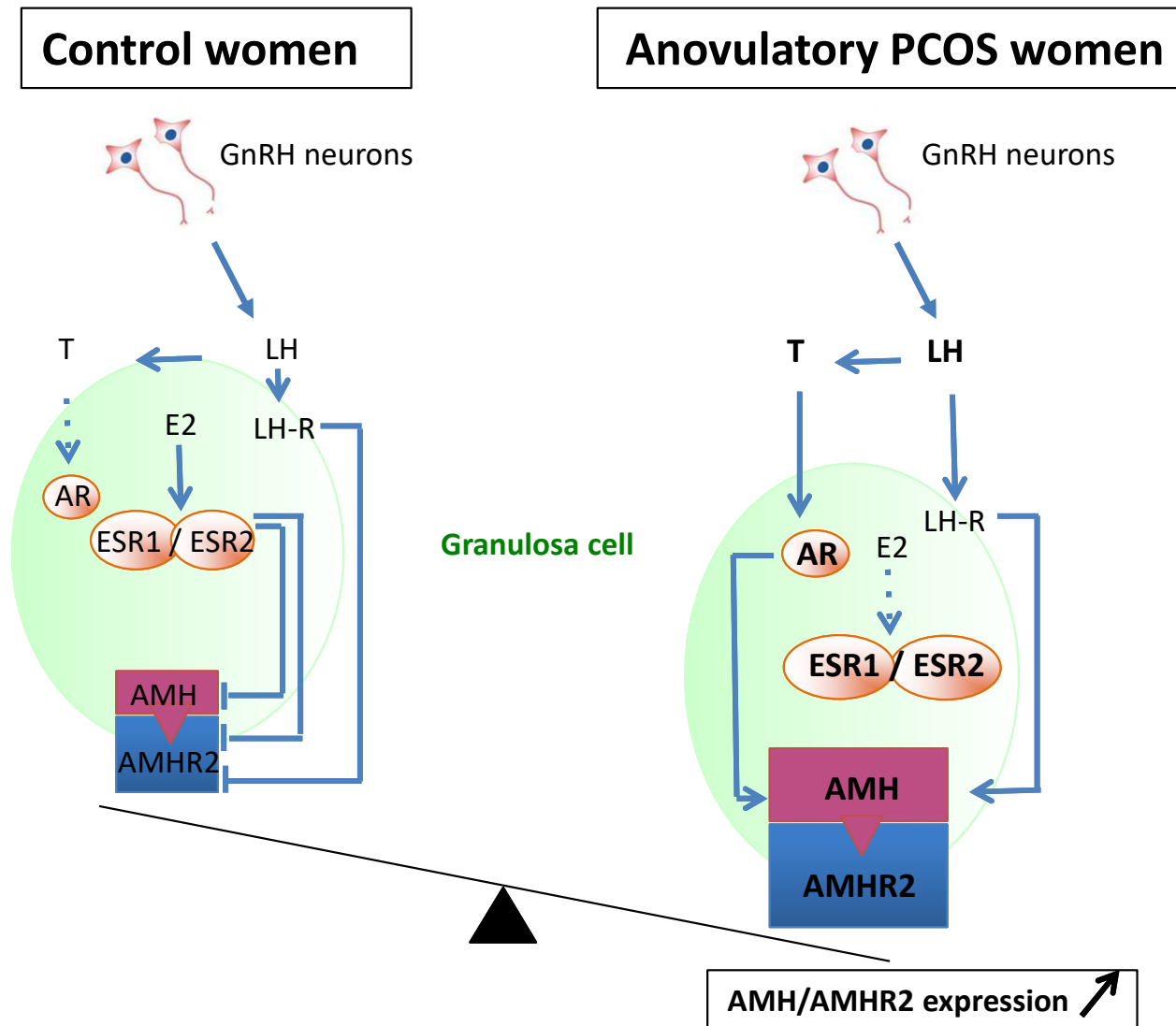
DHT

E2

Q RT PCR

AMH/AMHR2 mRNAs

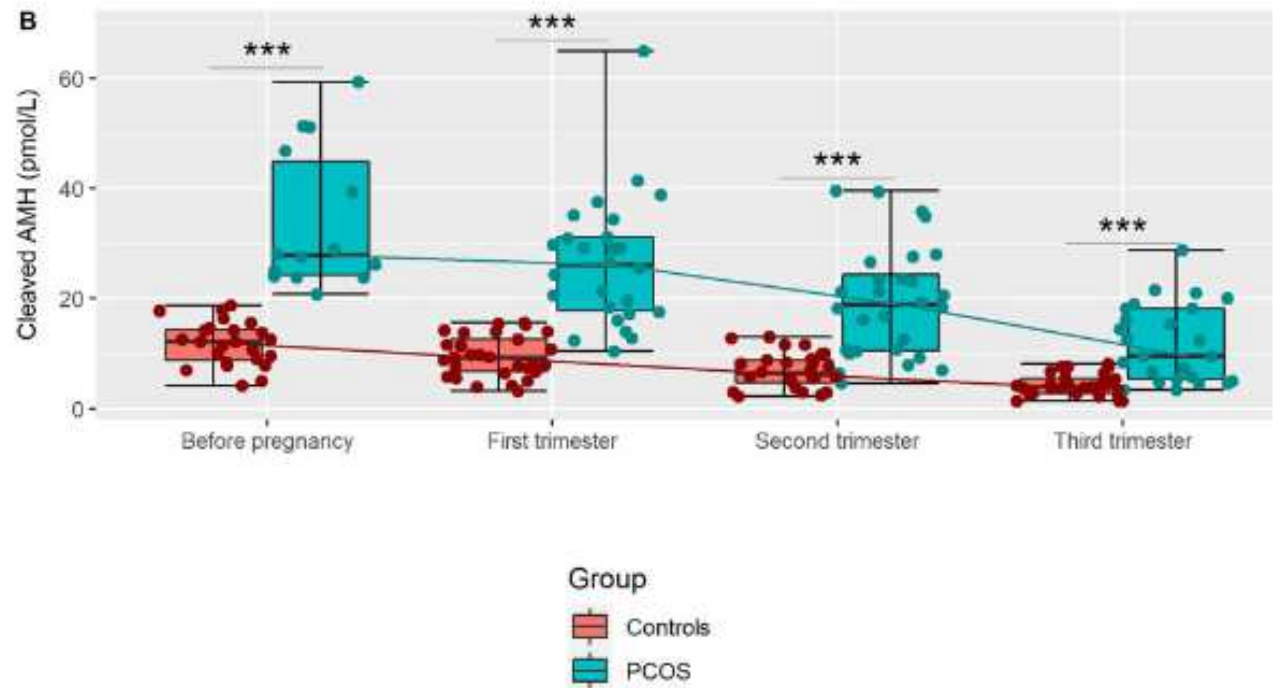
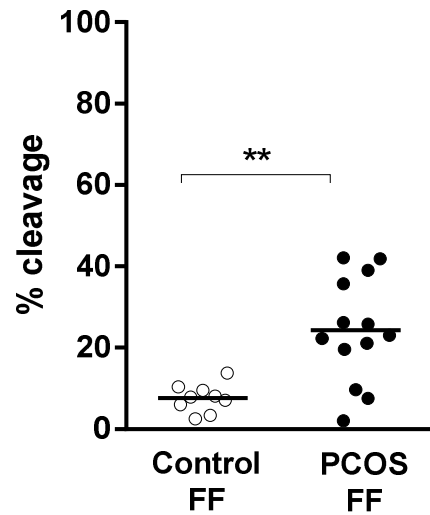
# Regulation of AMH/AMHR2 expression in human luteal granulosa cells



*Reviewed in di Clemente et al., 2021*

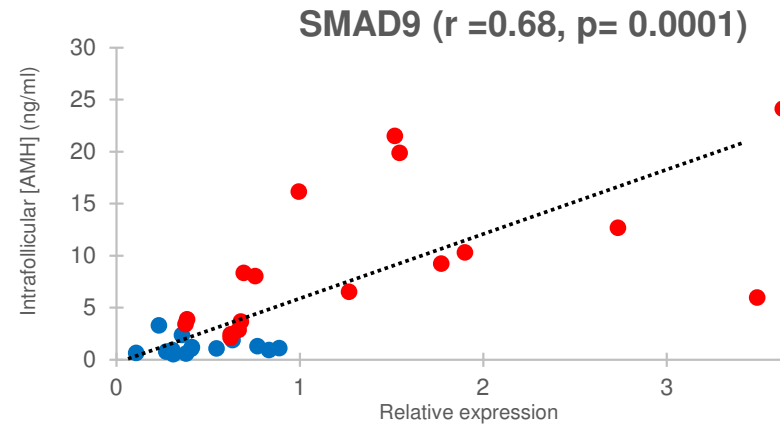
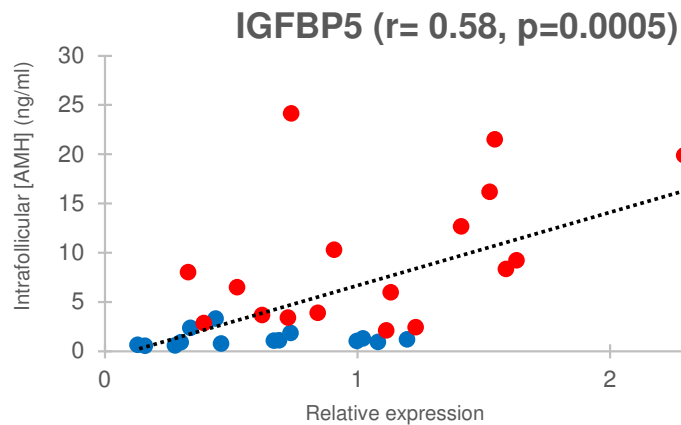
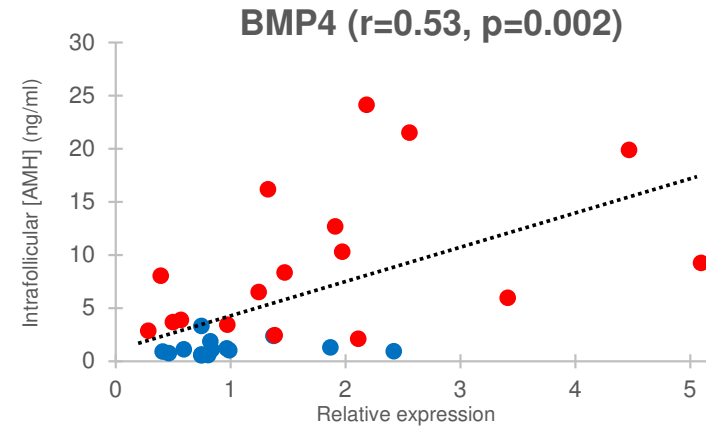
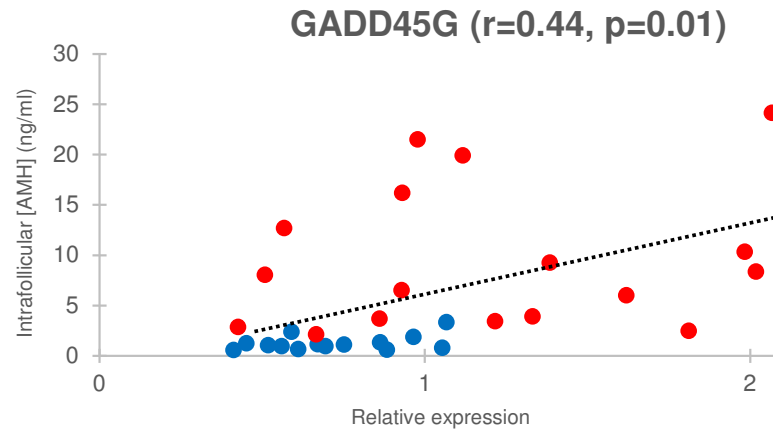


# More cleaved AMH in PCOS women

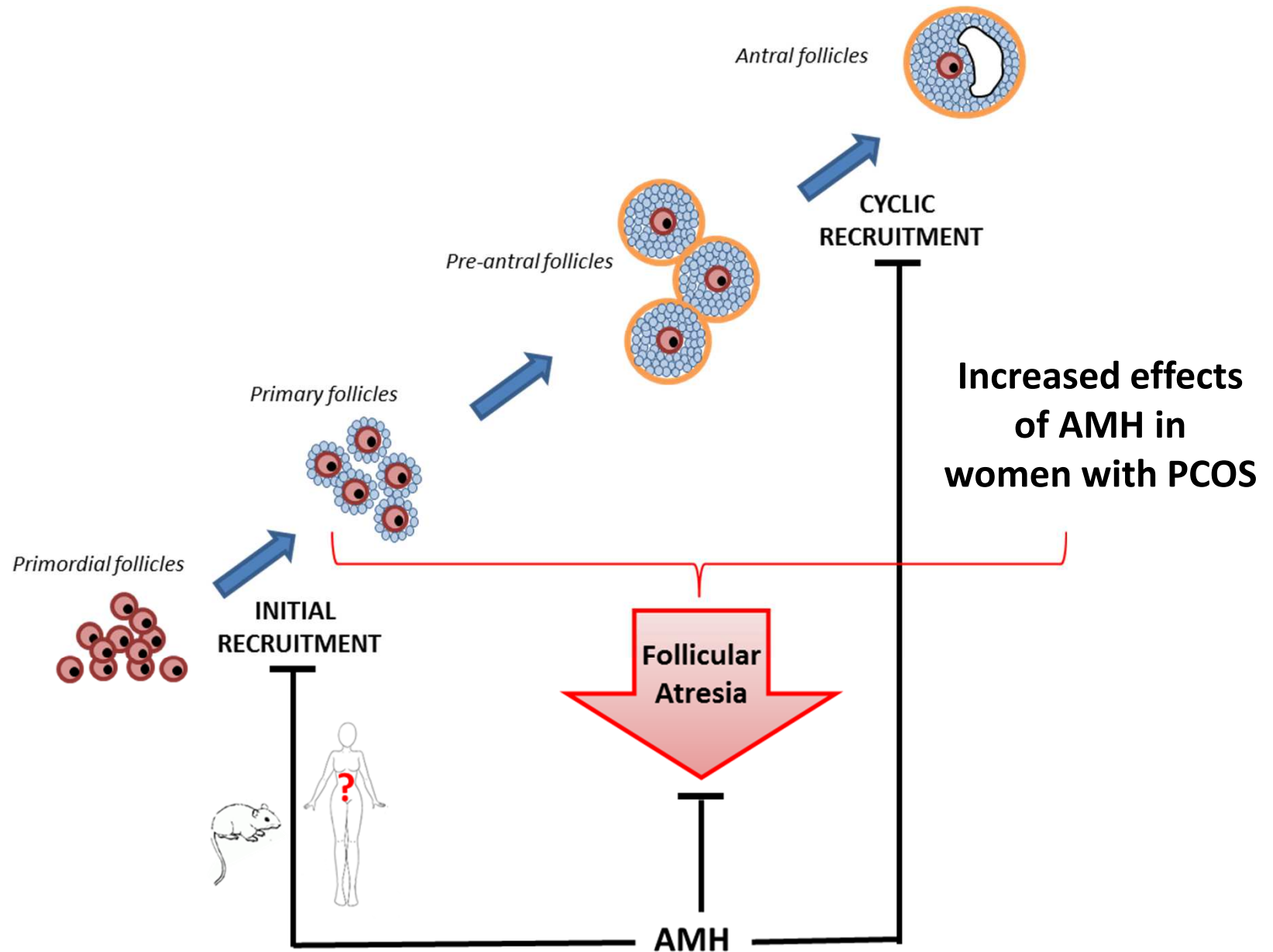


*Pierre et al., 2016*  
*Pankhurst et al., 2017*  
*Peigné et al., 2023*

# AMH target genes up-regulated in women with PCOS correlate with their FF AMH levels

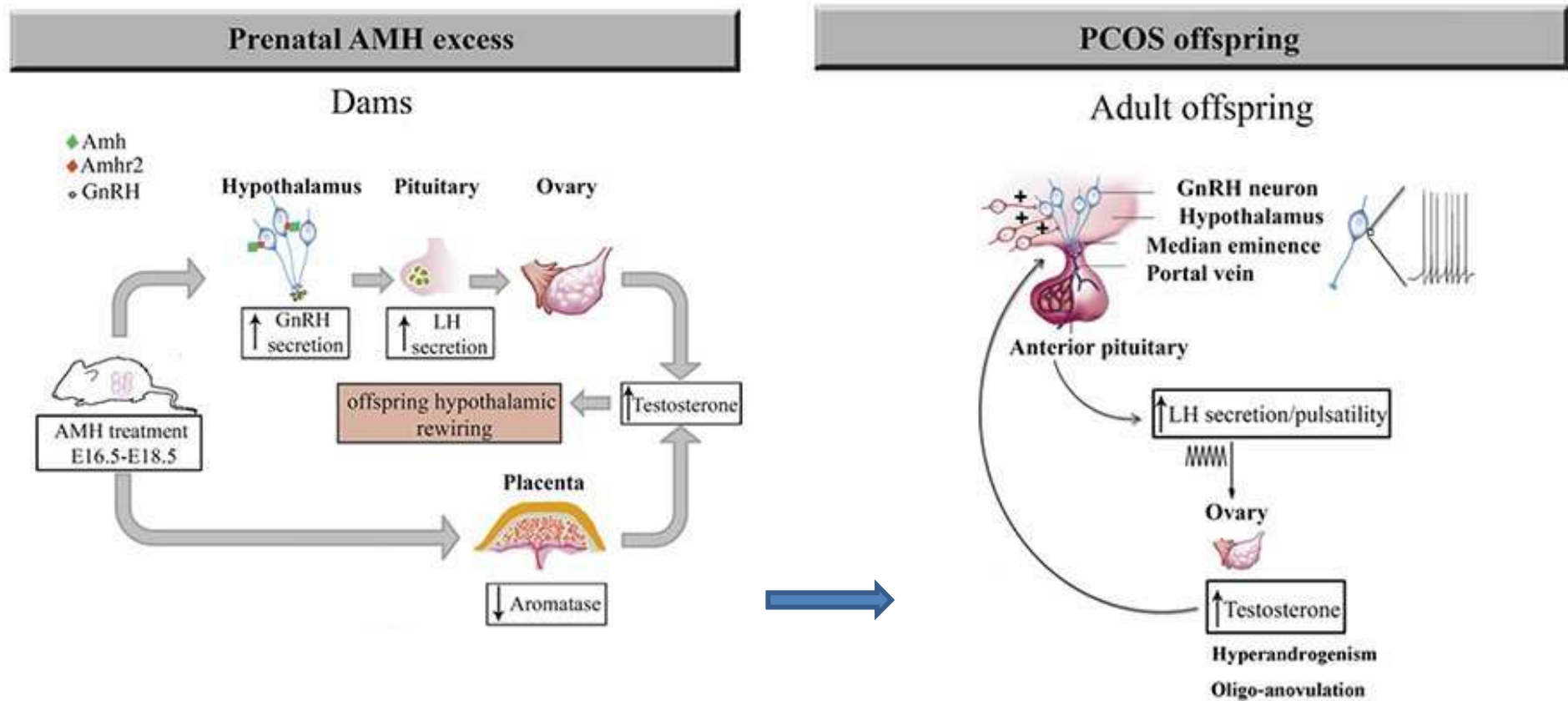


# AMH effects in the ovaries



*Reviewed in di Clemente et al., 2021*

# PAMH mice: fetal programming of the PCOS



*Tata et al., 2018, Barbotin et al., 2019,  
Mimouni et al., 2021, Silva et al, 2022*

# Goto-Kakizaki rats

Type 2 Diabetes model



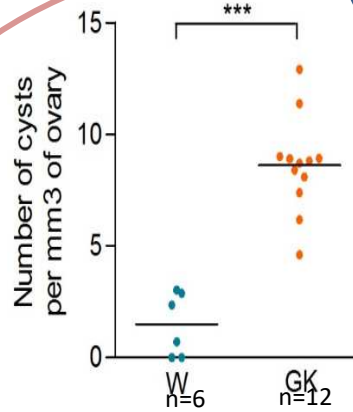
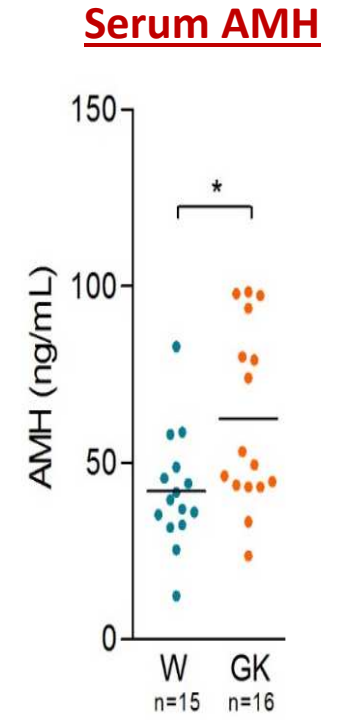
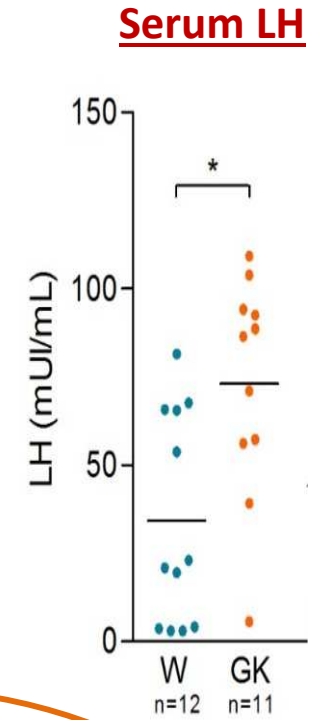
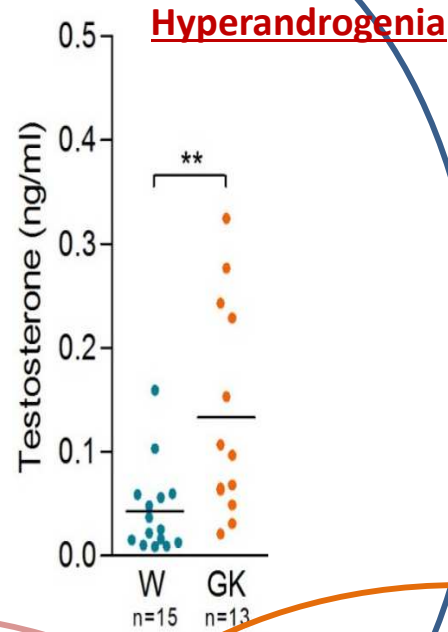
## Metabolic disorders:

- ✓ Hyperglycemia
- ✓ Glucose intolerance
- ✓ Insulin resistance
- ✓ Defective  $\beta$  cells mass
- ✓ Dyslipidemia

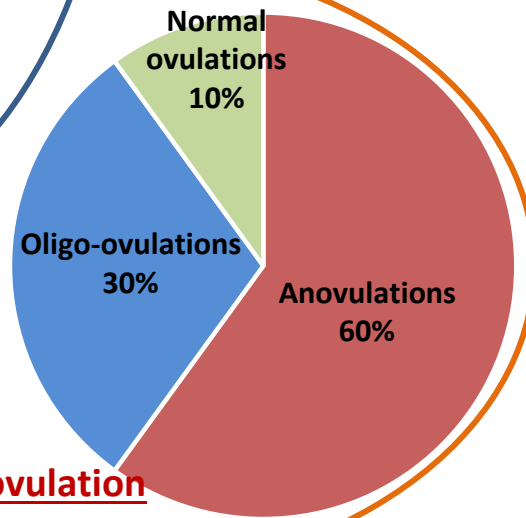
Goto et al., 1976

# Goto-Kakizaki rats

● Wistar  
● GK



**Phenotype 1**

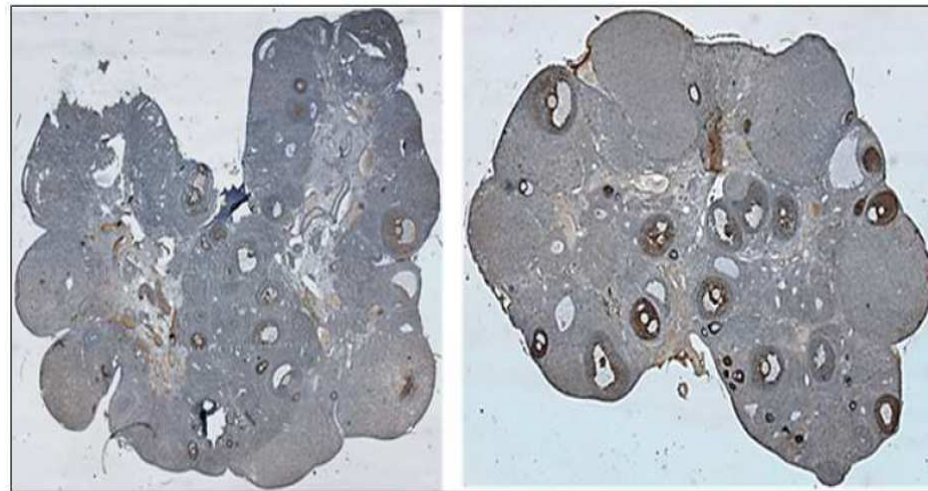


# AMH in GK rats

## AMH protein

Wistar

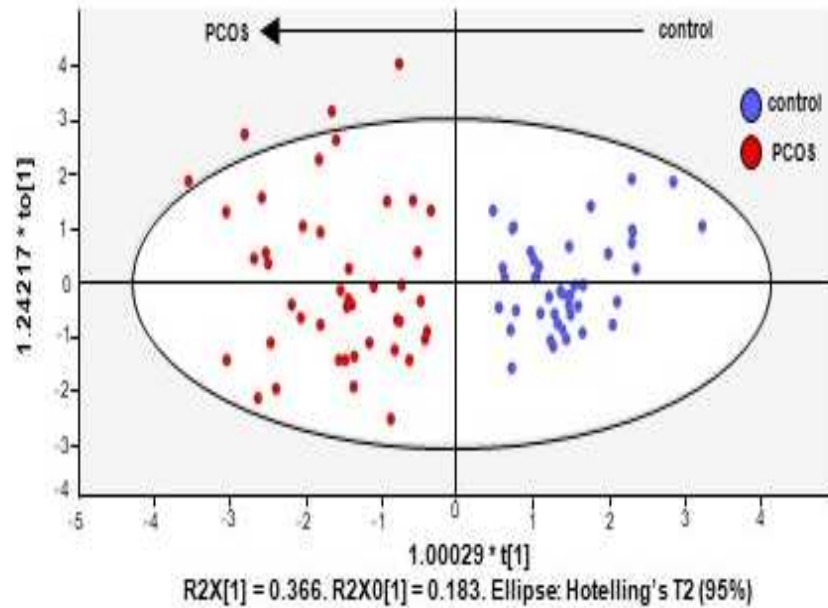
GK



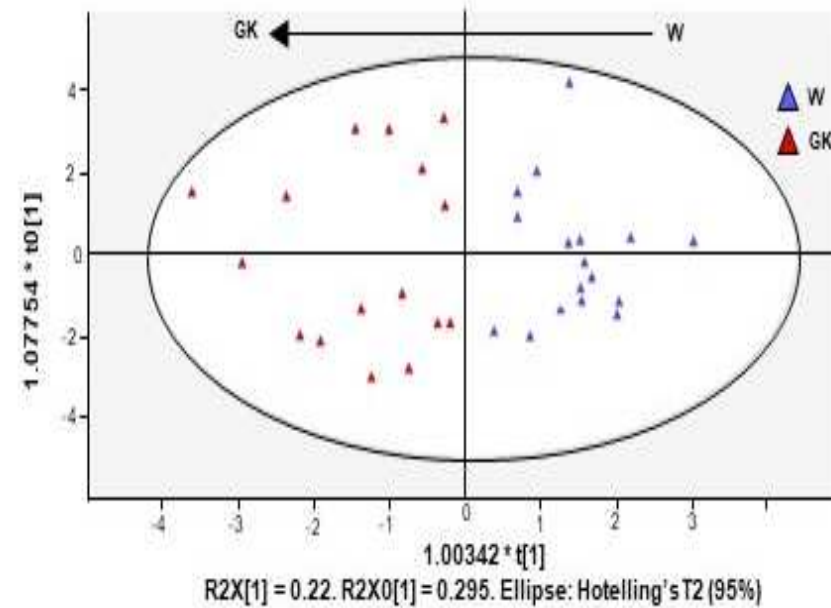
*Bourgneuf et al, 2021*

# Goto-Kakizaki rats

Women with PCOS/controls



GK rats/Wistar



Hôpital Tenon (CPP PREFENDO 18.10.58)

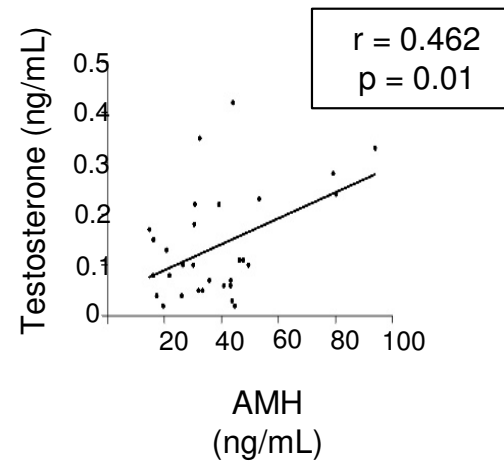
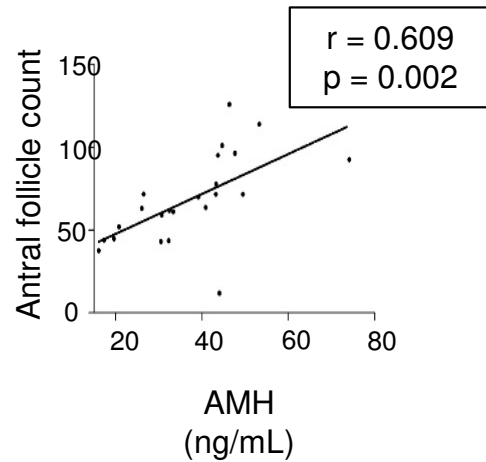
Reproductive criteria used for the analysis: AFC, serum AMH, LH and E2 levels, intrafollicular androgens and progesterone levels

*Bourgneuf et al., 2021*

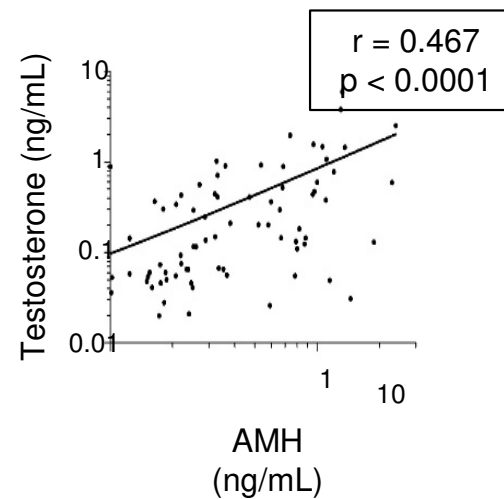
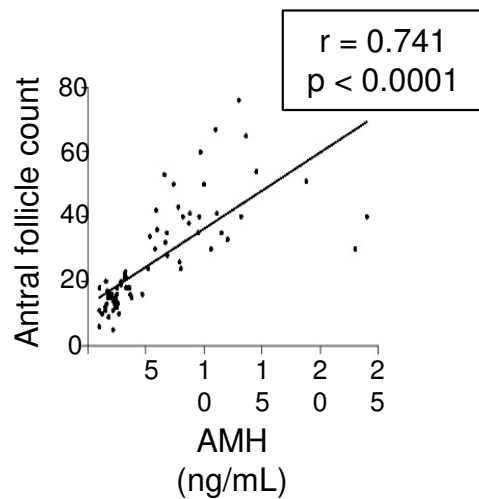


# AMH in GK rats

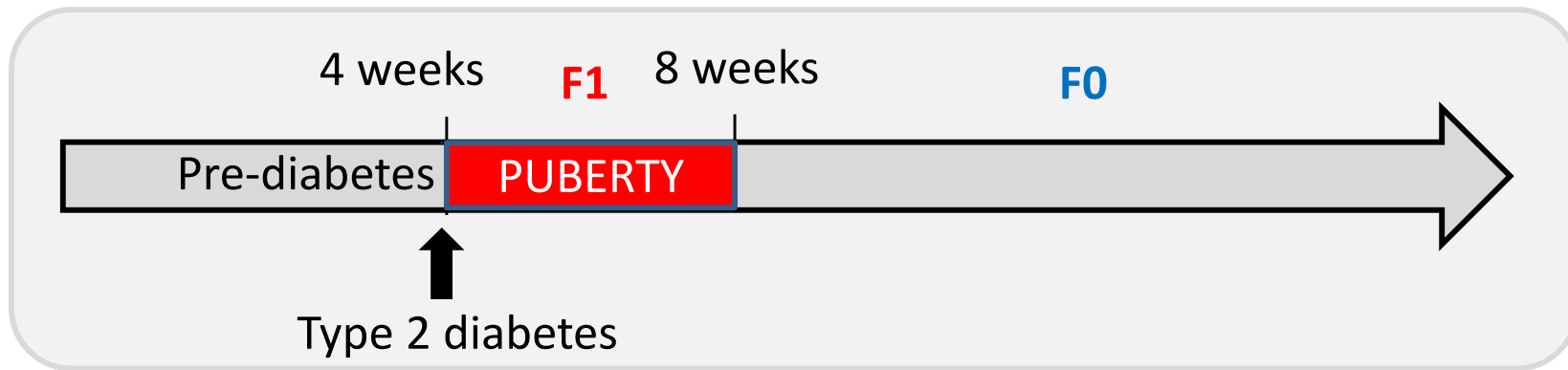
## GK rats/Wistar



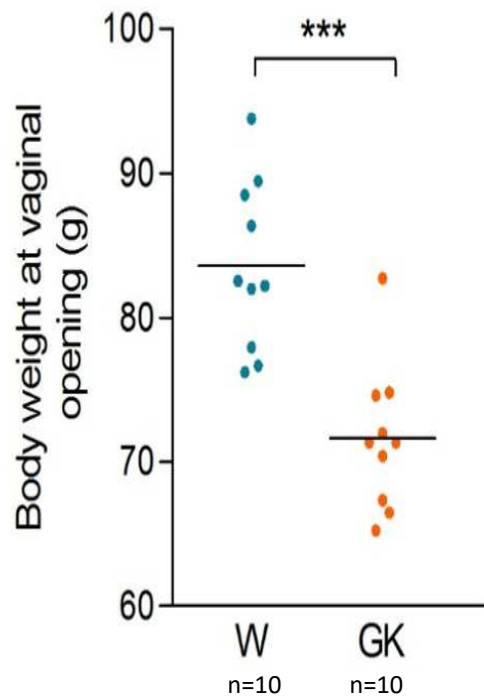
## Women with PCOS/controls



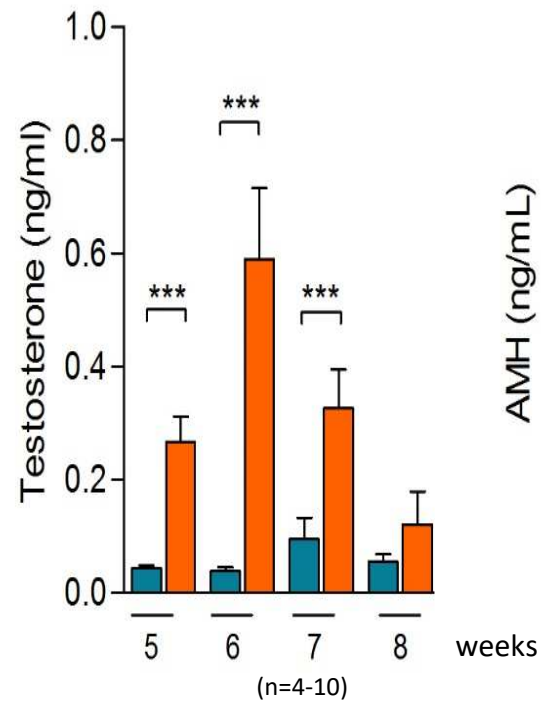
# AMH in GK rats



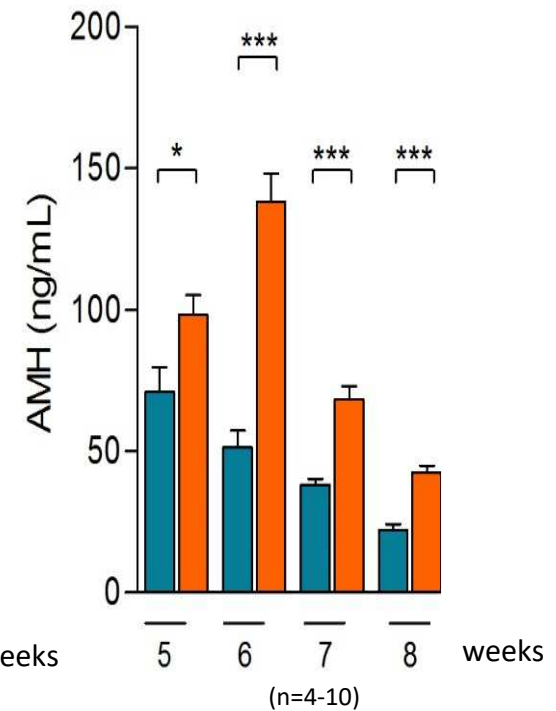
## Precocious puberty



## Hyperandrogenia



## High AMH levels



- Wistar
- GK

**Camille Bourgneuf**  
**Charlotte Dupont**  
**Rachel Levy**  
**Emmanuelle Mathieu D'Argent**  
**Bruno Fève**  
**Chrystèle Racine**

## Collaborations

**Unité Biologie Fonctionnelle et Adaptative**

Jamileh Movassat

Danielle Bailbé

**Centre de Recherche Saint**

**Antoine**

Antonin Lamaziere

Dominique Farabos

**INRAE**

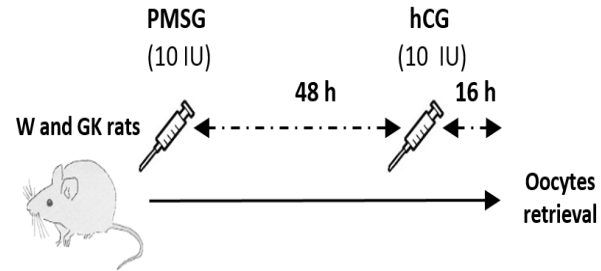
Danielle Monniaux

## AMH/AMHR2 polymorphisms/mutants which reduce their activity

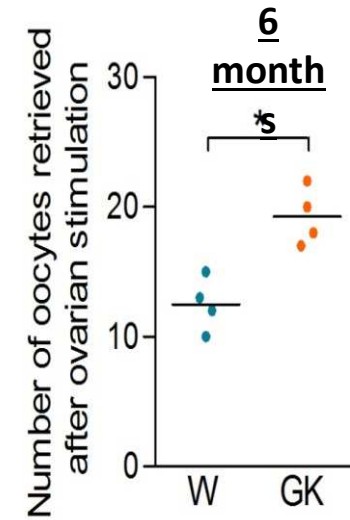
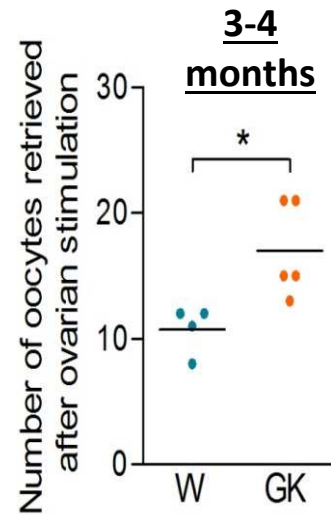
- AMH Ile49Ser et AMHR-II -482 A/G (*Kevenaar et al. 2007*)
  - E2 levels in follicular phase >
  - Menopause 2.6 years earlier
  - Follicle number and androgens < in women with PCOS
- AMH G264R, D288E, R444H (*Mercadal et al. 2015*)
  - Induce POI
- AMH and AMHR2 variants (*Gorsic et al. 2017 and 2019*)
  - PCOS-specific
- Rs10406324 AMH (*Moolhuijsen et al., 2022*)
  - Lower AMH levels in women with PCOS

# Goto-Kakizaki rats

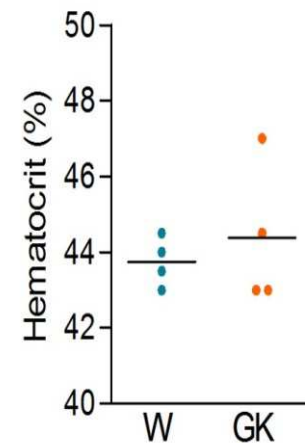
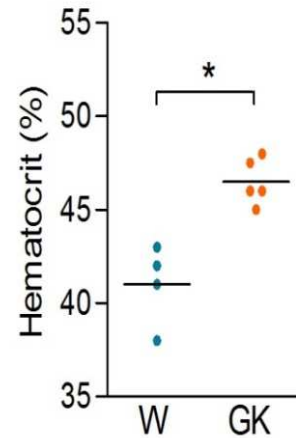
## Ovarian stimulation



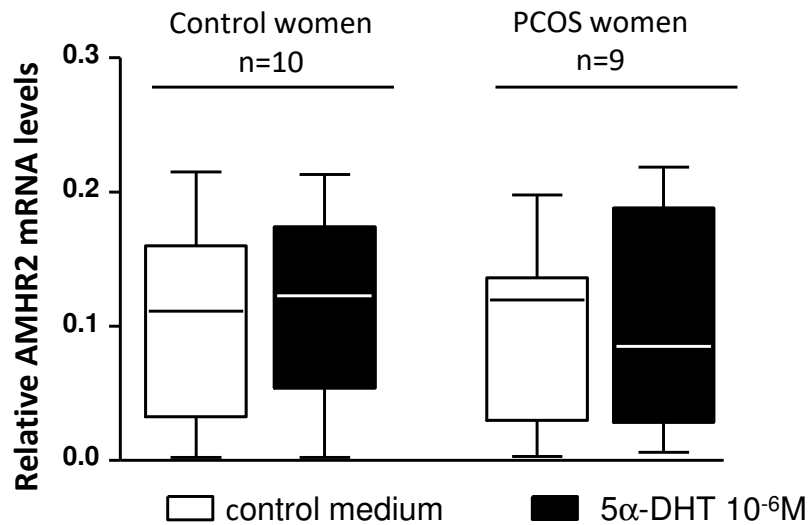
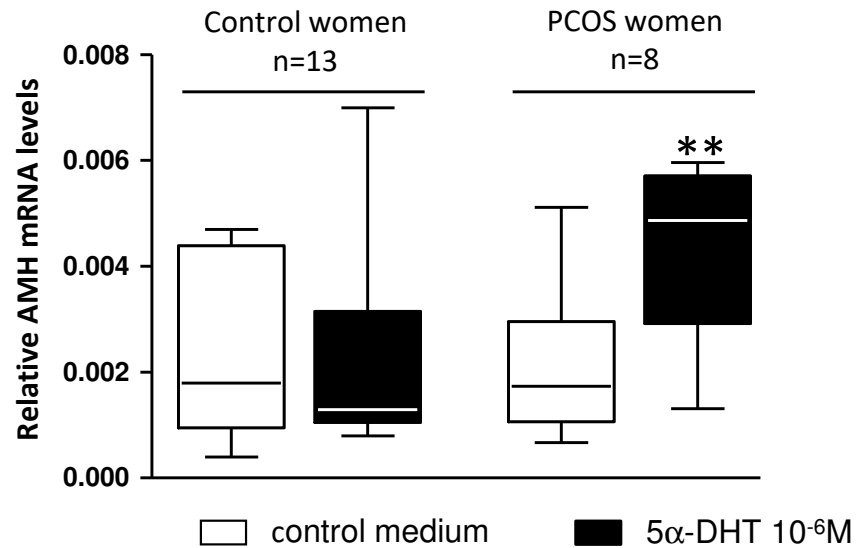
## Number of oocytes



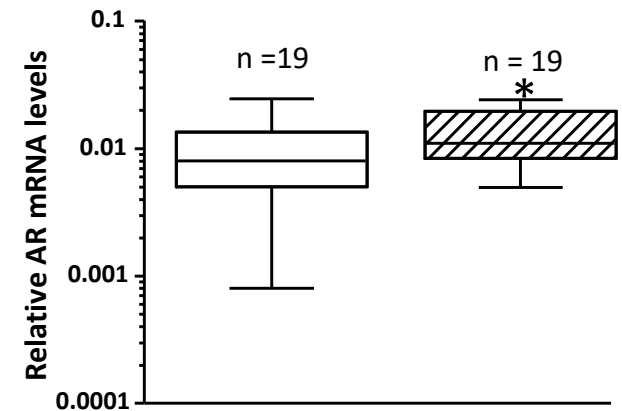
## Hematocrit



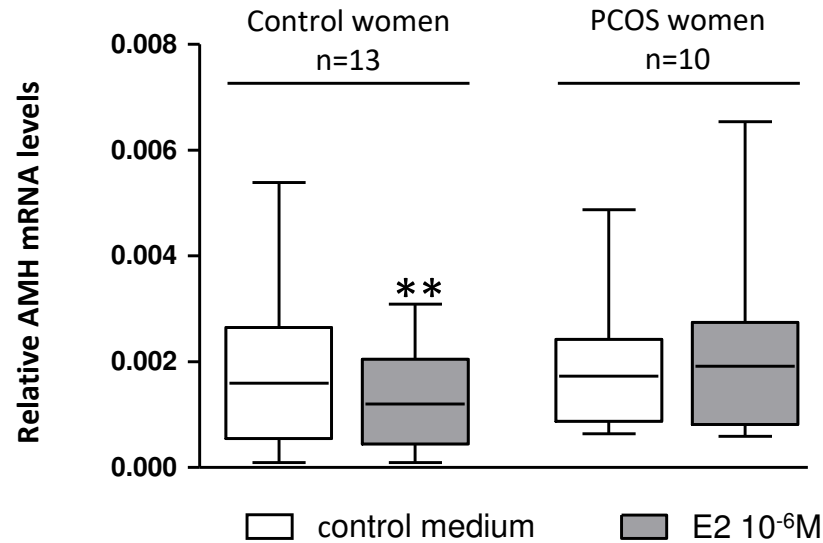
# Regulation of ovarian AMH by androgens in granulosa cells from PCOS women



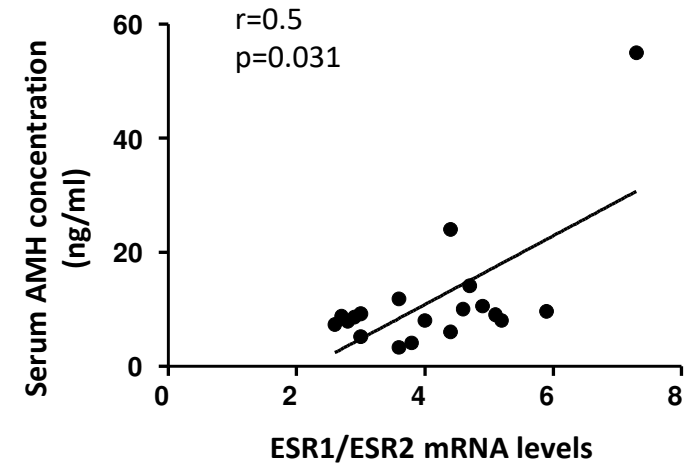
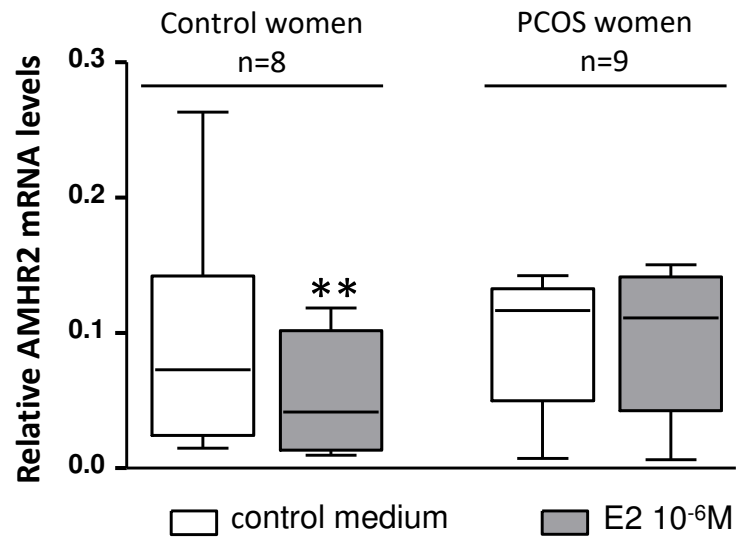
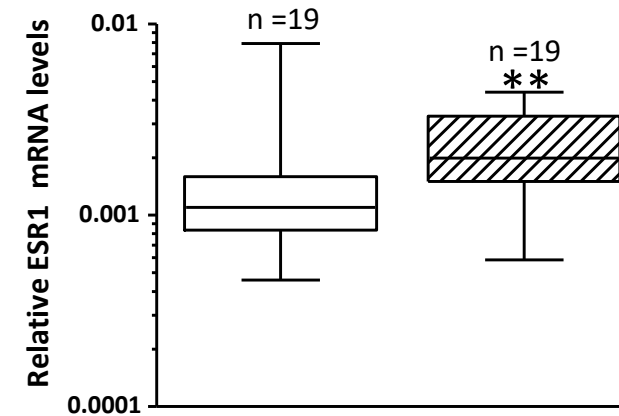
## Expression of AR



# Regulation of ovarian AMH by estradiol in granulosa cells from PCOS women

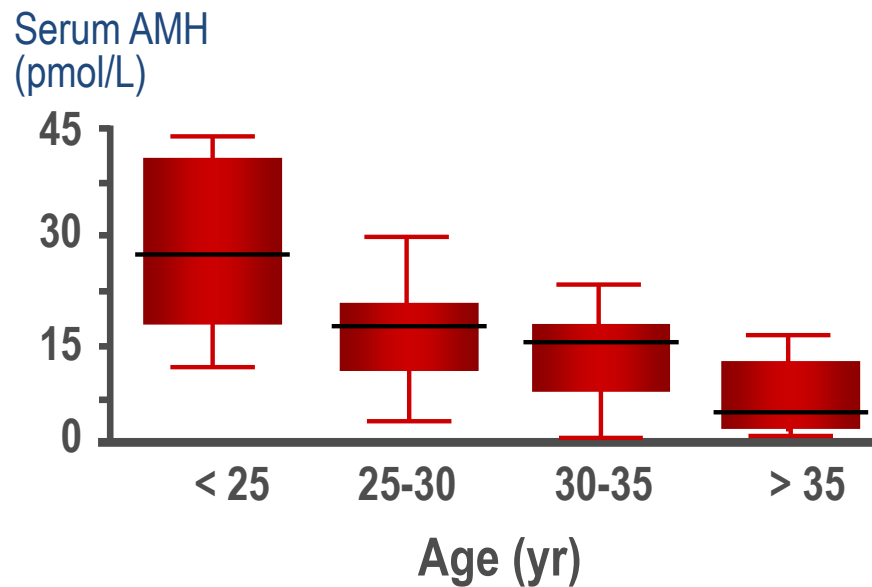


## Expression of ESR1 and ESR2

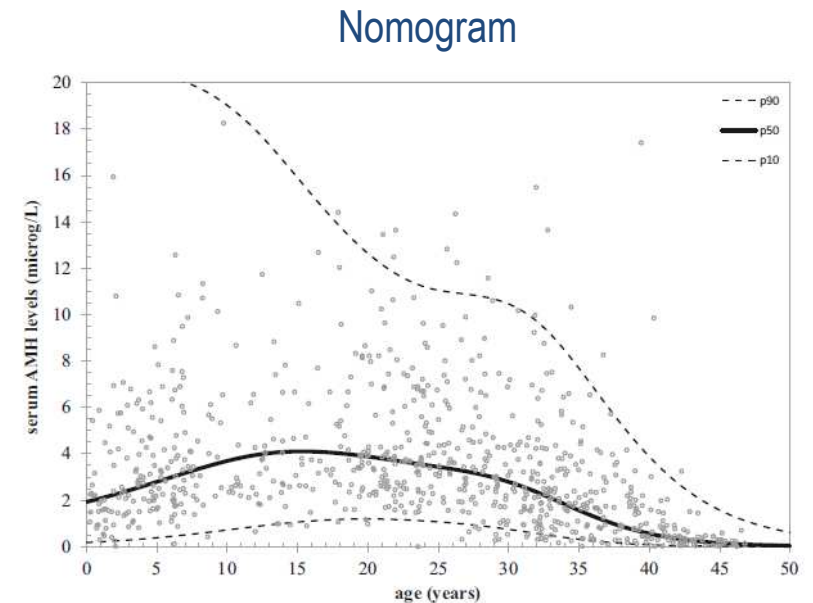


# AMH: A MARKER OF OVARIAN RESERVE

## AMH during reproductive life



De Vet et al., 2002

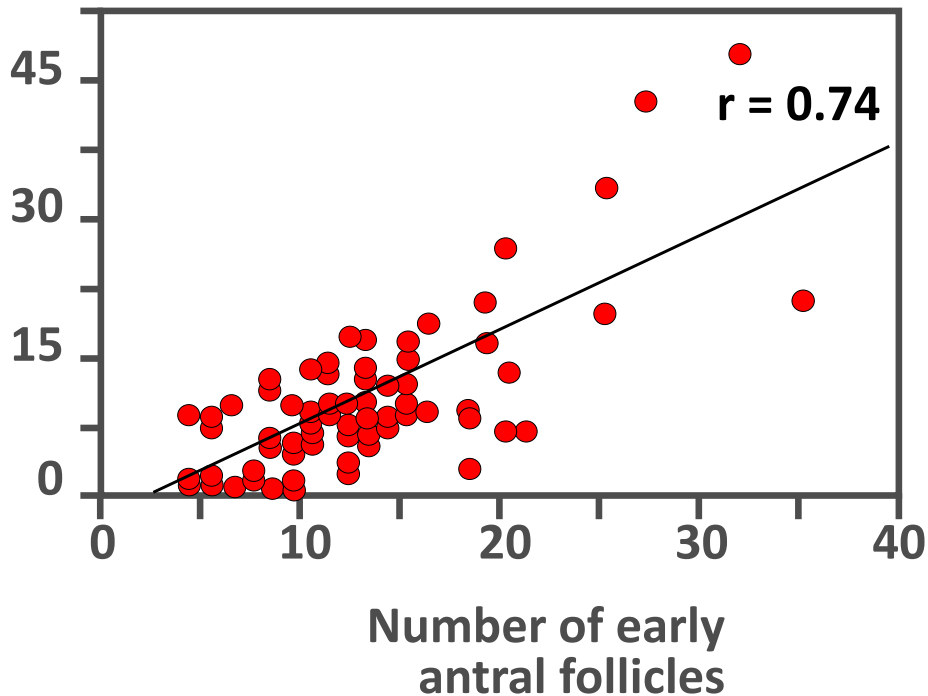


Lie Fong et al., 2012



# AMH: A MARKER OF OVARIAN RESERVE

Serum AMH  
(pmol/L)



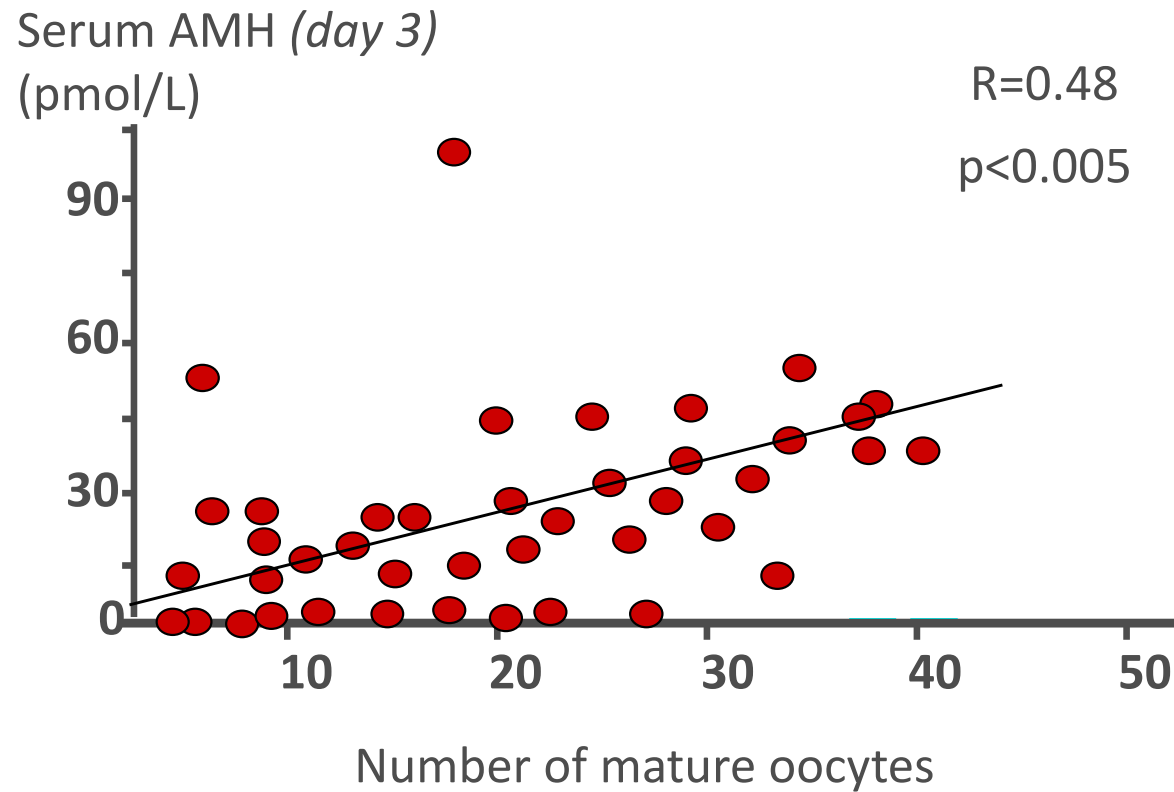
Number of early  
antral follicle

vs.	r	p
AMH	0.74	0.0001
Inh B	0.29	0.001
FSH	-0.29	0.001
LH	0.05	NS
E2	-0.08	NS

Fanchin et al., 2003  
Van Rooij et al., 2002

# AMH: A PRONOSTIC MARKER OF IVF

A marker of ovarian responsiveness

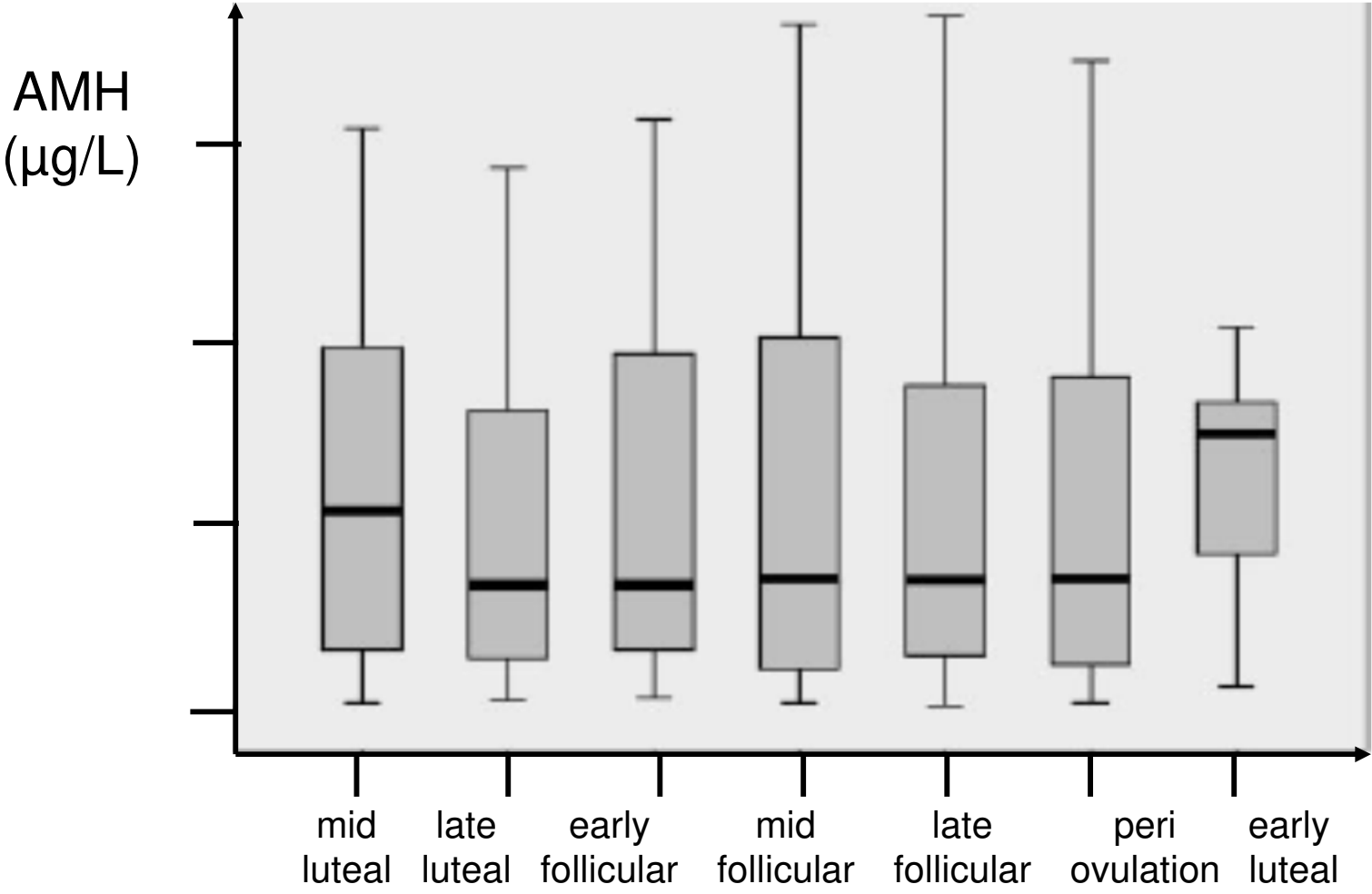


Seifer et al., 2002

# AMH: A PRONOSTIC MARKER OF PREGNANCY

- **Contradictory results:**
- In ART:
  - \* generally positively correlated with AMH,
  - \* but it is more a problem of cut-off
- In the general population:
  - \* generally positively correlated with AMH in women with regular cycles,
  - \* but depends more on age

# SERUM AMH DURING MENSTRUAL CYCLE



*Hehenkamp et al., 2006, Gracia et al, 2018*