

# KRONİK ANOVULASYON FİZYOPATOLOJİSİ VE PCOS'DA FOLLİKÜL GELİŞİMİ



PROF. DR. SEFA KELEKÇİ  
İZMİR KATİP ÇELEBİ ÜNİVERSİTESİ, TIP FAKÜLTESİ,  
KADIN HASTALIKLARI VE DOĞUM AD



# PLAN

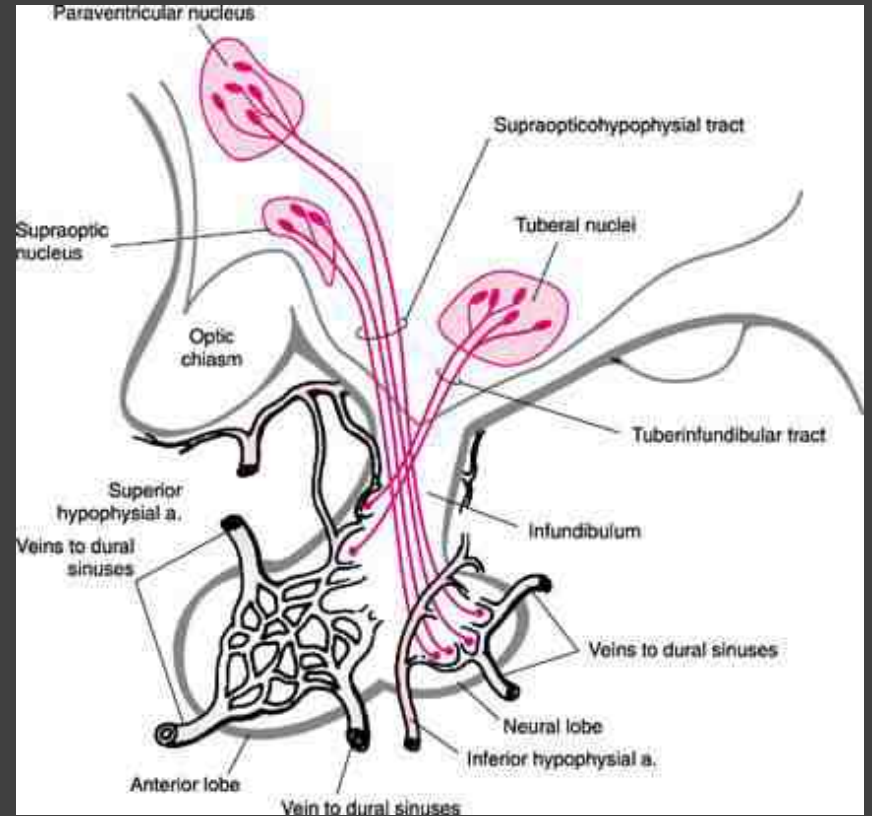
- ANOVULASYON SINIFLAMA
- ANOVULASYON PATOGENEZİ
- NORMAL FOLLİKÜLOGENEZİS
- PCOS
- PCOS'DA FOLLİKÜL DİNAMİĞİ
- SONUÇ

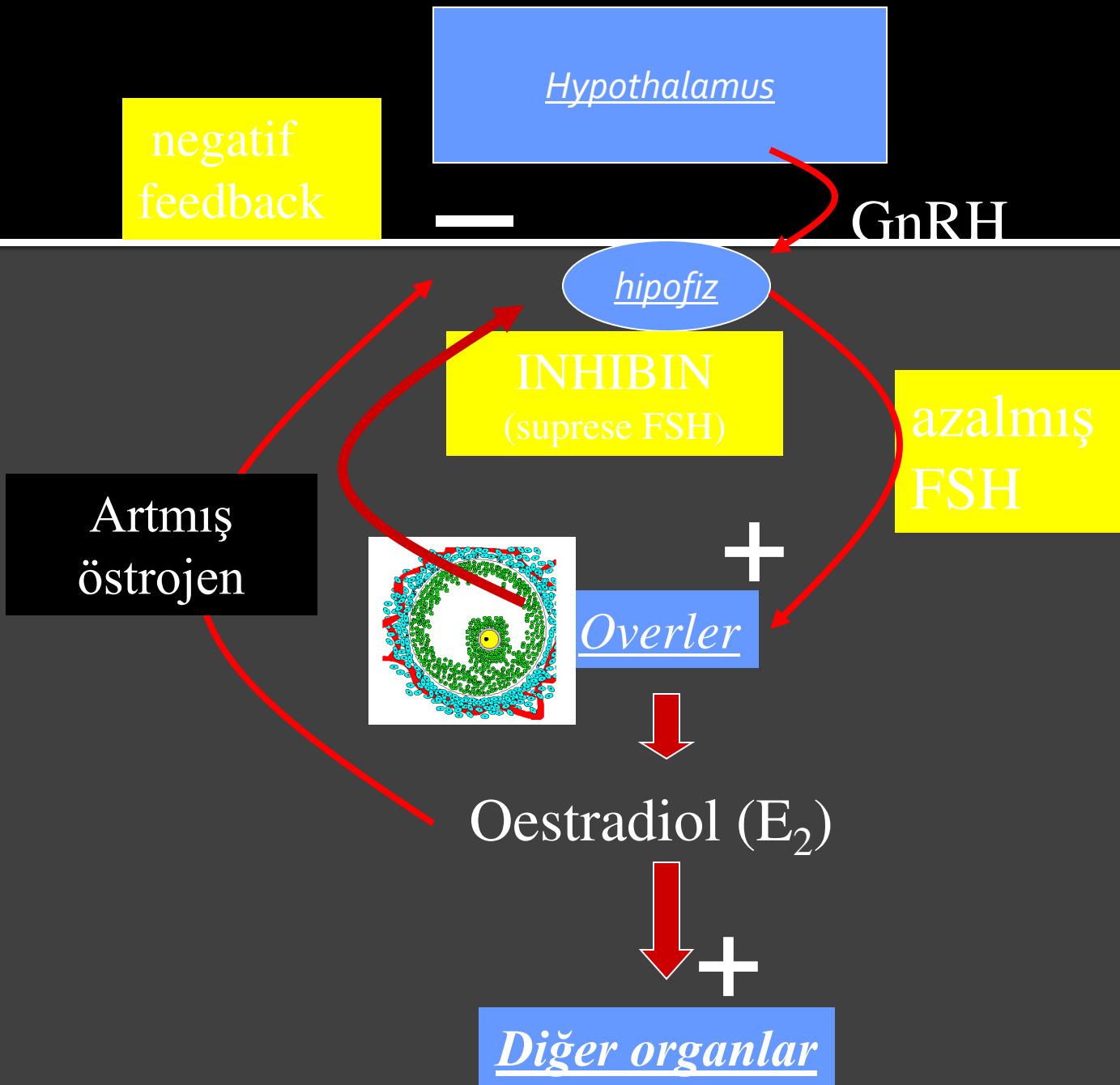
# KRONİK ANOVULASYON

- ALTI AYDAN YA DA ÜÇ SIKLUSDAN DAHA UZUN SÜRE OVULASYONUN OLMAMASI
- KESİTSEL BİR ÇALIŞMADA KRONİK ANOVULASYONU OLANLARIN %75'İNDE PCO MORFOLOJİSİ

# NORMAL OVULASYON

- HİPOTALAMO-HİPOFİZER AKS
- FEED-BACK SİNYALLER
- OTOKRİN VE PARAKRİN PEPTİDLER





# SINIFLAMA

- **GRUP I: HİPOTALAMO-HİPOFİZER YETMEZLİK**
  - FSH ↓
  - E2 ↓
- **GRUP II: HİPOTALAMO-HİPOFİZER DİSFONKSİYON**
  - FSH N
  - E2 N
- **GRUP III: OVARIAN YETMEZLİK**
  - FSH ↑
  - E2 ↓

WHO, 1976

# ANOVULASYON PATOGENEZİSİ-1

- SANTRAL DEFEKTLER
  - GNRH PULSALİTE PROBLEMLERİ
    - STRESS, ANKSİYETE, AKUT KİLO KAYBI
  - EPİLEPSİ
  - HİPERPROLAKTİNEMİ
  - PCOS (AMPİTÜDE, SIKLIK)

# ANOVULASYON PATOGENEZİSİ-2

- ANORMAL FEED-BACK SİNYALLERİ
  - FSH STİMULASYON KAYBI
    - PERSİSTE ÖSTROJEN SEKRESYONU
    - ANORMAL ÖSTROJEN KLİRENSİ VE METABOLİZMASI
    - EKSTRAGLANDÜLER ÖSTROJEN ÜRETİMİ
  - LH STİMULASYON KAYBI

# ANOVULASYON PATOGENEZİSİ-3

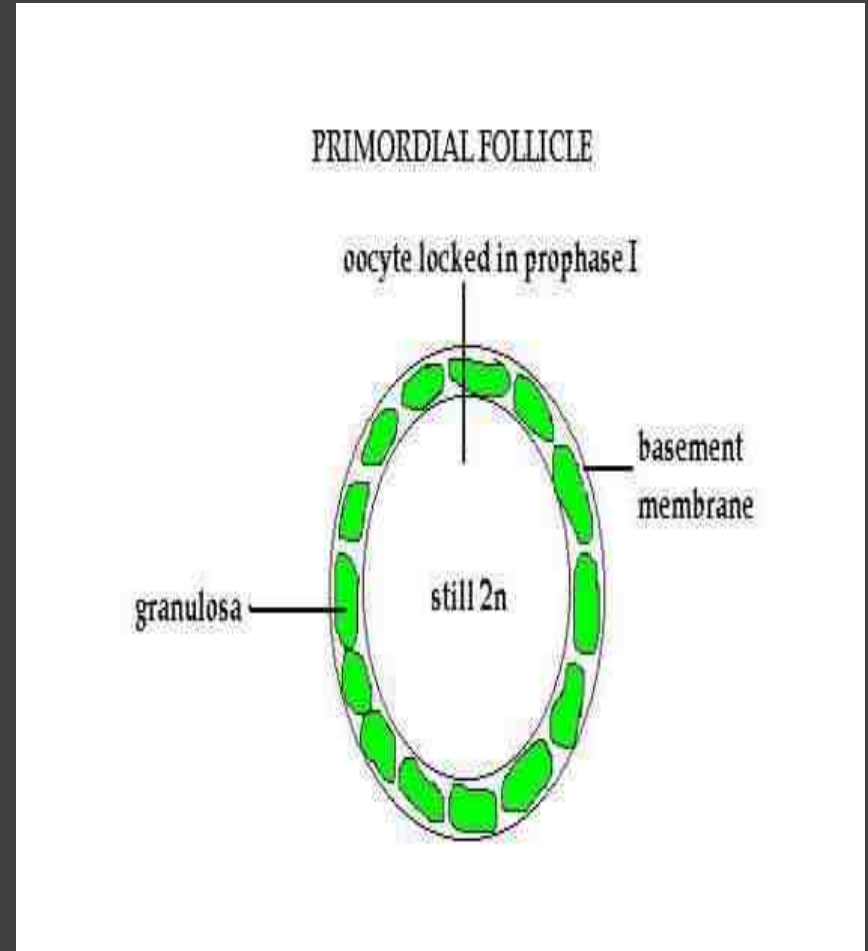
- LOKAL OVARIAN FAKTÖRLER
  - OTOKRİN/PARAKRİN PEPTİDLER
  - IGF-II: GONADOTROPİN UYARISINA CEVABEN TEKA HÜCRELERİNDEN SALINIR. BU E2 VE GROWTH HORMON İLE ARTIRILIR. LH BAĞIMLI ANDROJEN SENTEZİNİ ARTIRIR.
  - IGF-II GRANÜLOZA HÜCRE PROLİFERASYONU, AROMATAZ AKTİVİTE VE PROGESTERON SENTEZİNİ UYARIR
  - AKTİVİN
  - İNHİBİN

# ANOVULASYON PATOGENEZİSİ-4

- AŞIRI KİLO
  - ANDROJENLERİN ÖSTROJENE PERİFERİK AROMATİZASYONUNU ARTIRIR.
  - SHBG ↓ SERBEST E2 VE TESTOSTERON ARTIŞINA SEBEB OLUR
  - ARTMIŞ İNSÜLİN SEVİYESİ OVARIAN STROMAL DOKUDA ANDROJEN ÜRETİMİNİ UYARIR

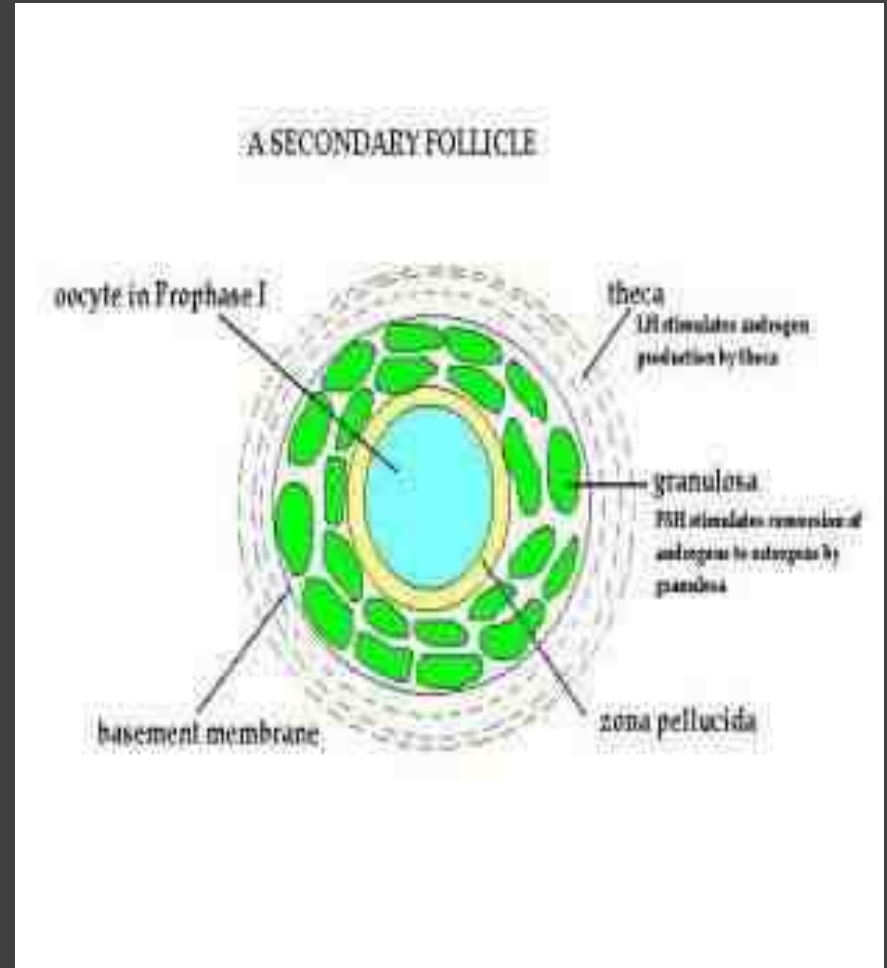
# FOLLİKÜLOGENEZİS- HATIRLATMA

- PRIMORDIAL FOLLİKÜL
  - TEK SIRA GRANÜLOZA HÜCRELERİ(SKUAMOZ)
  - OOSİT MI
  - BASAL MEMBRAN
  - STABİL



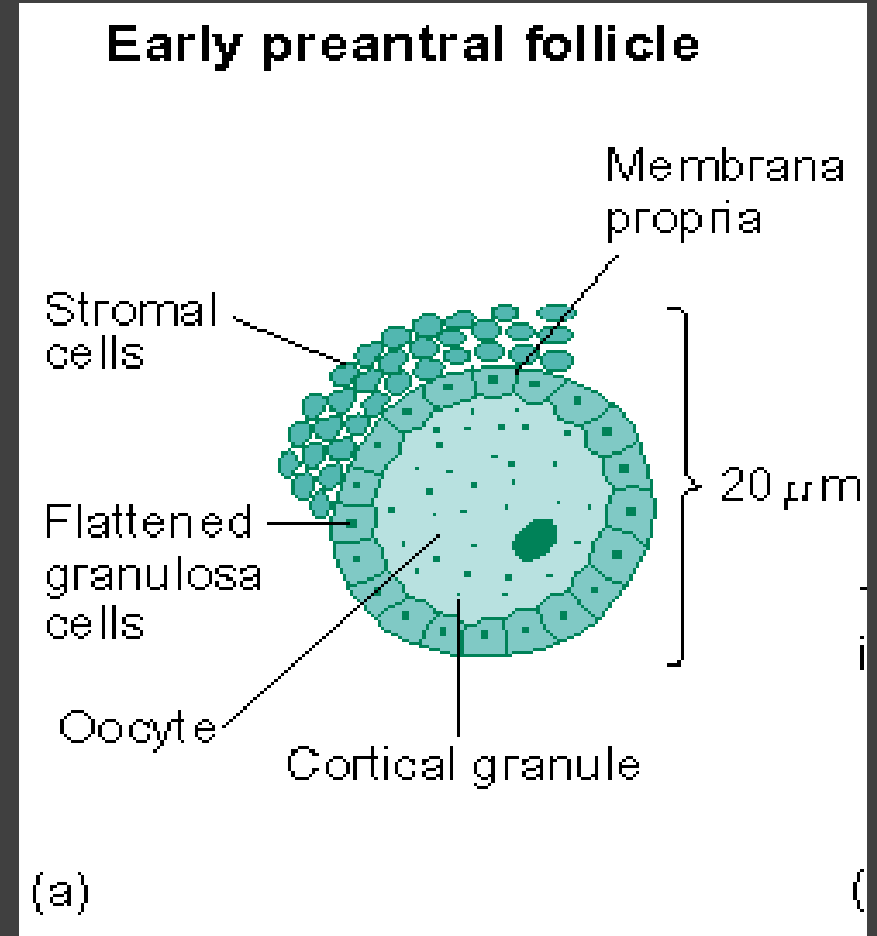
# FOLLİKÜLOGENEZİS- HATIRLATMA

- SEKONDER FOLLİKÜL
  - OOSİT MI
  - GRANULOSA HÜCRE PROLİFERASYONU
  - ZONA PELLUCIDA
  - BÜYÜME MEVCUT
  - TEKA İNTERNA DİFERANSİYASYONU



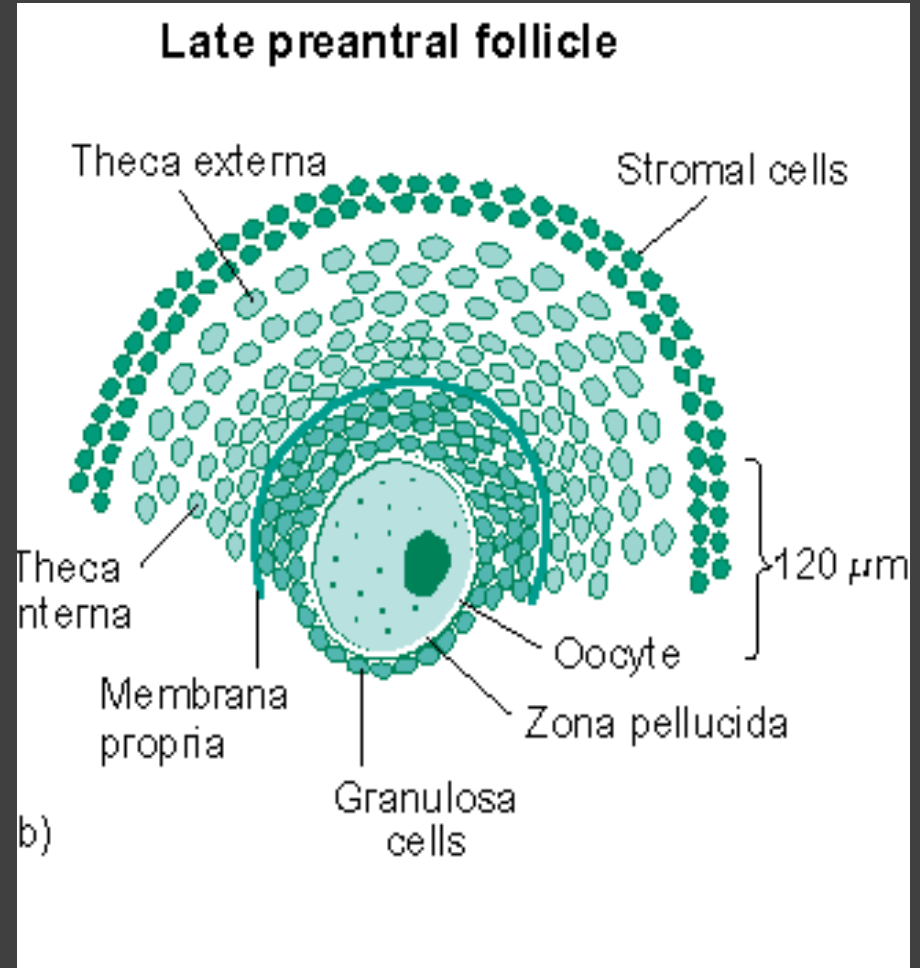
# FOLLİKÜLOGENEZİS- HATIRLATMA

- ERKEN PRENATAL FOLLİKÜLER
  - OOSİTTE CORTICAL GRANÜLLEŞME
  - MATURASYON
  - TEKA EKSTERNA DİFERANSİYASYONU
  - BÜYÜME



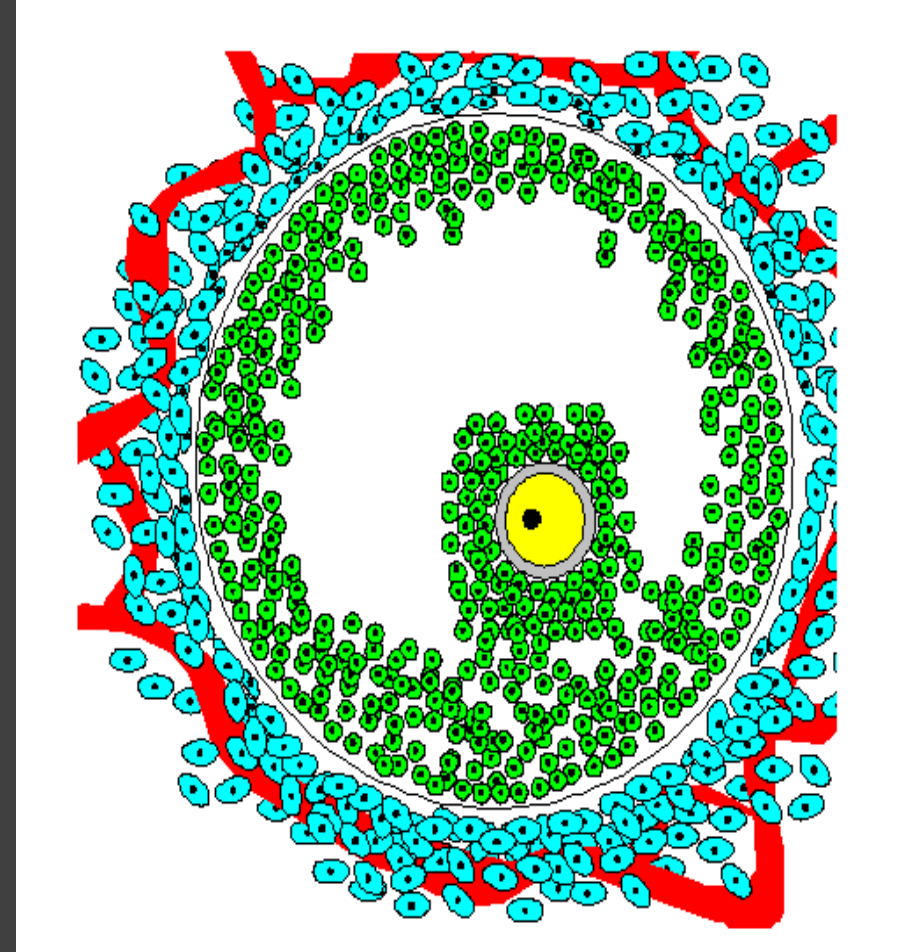
# FOLLİKÜLOGENEZİS- HATIRLATMA

- GEÇ PREANTRAL FOLLİKÜL
  - GRANÜLOSA VE TEKA HÜCRE PROLİFERASYONU
  - BÜYÜME
  - MATURASYON
  - GÖRÜNTÜLENEBİLİR



# FOLLİKÜLOGENEZİS- HATIRLATMA

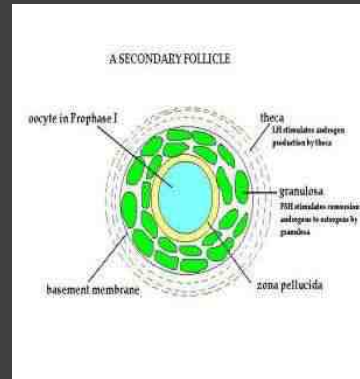
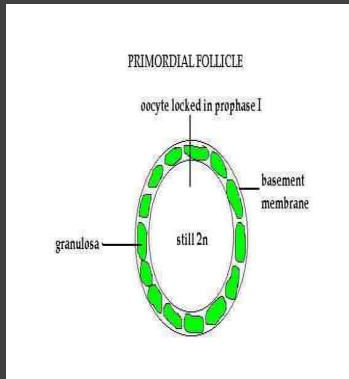
- GRAFT FOLLİKÜL
  - DOMİNANT
  - ANTRUM
  - CUMULUS HÜCRELERİ
  - PREEVULATUAR
  - 20 MM
  - SON MATURASYON



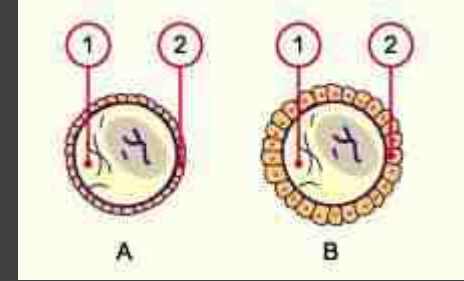
# NORMAL FOLİKÜLOGENEZIS-I



- İLK SEÇİM VE OTONOM BÜYÜME
  - FOLLİKÜLER BÜYÜMENİN BAŞLAMASI
  - TGF- $\beta$  PEPTİDLERİ



# PRİMORDİAL FOLLİKÜL AKTİVASYONU



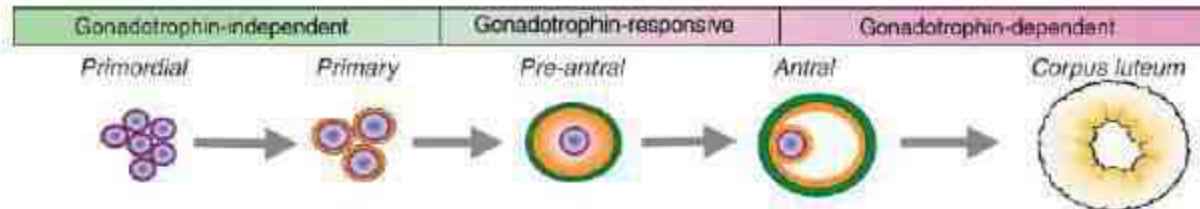
Aktivatörler

İnhibitörler

- KIT (tirozin kinaz reseptör)
- KL (KIT ligand)
- GDF-9
- BMP 4,7,15
- FGF2
- LIF

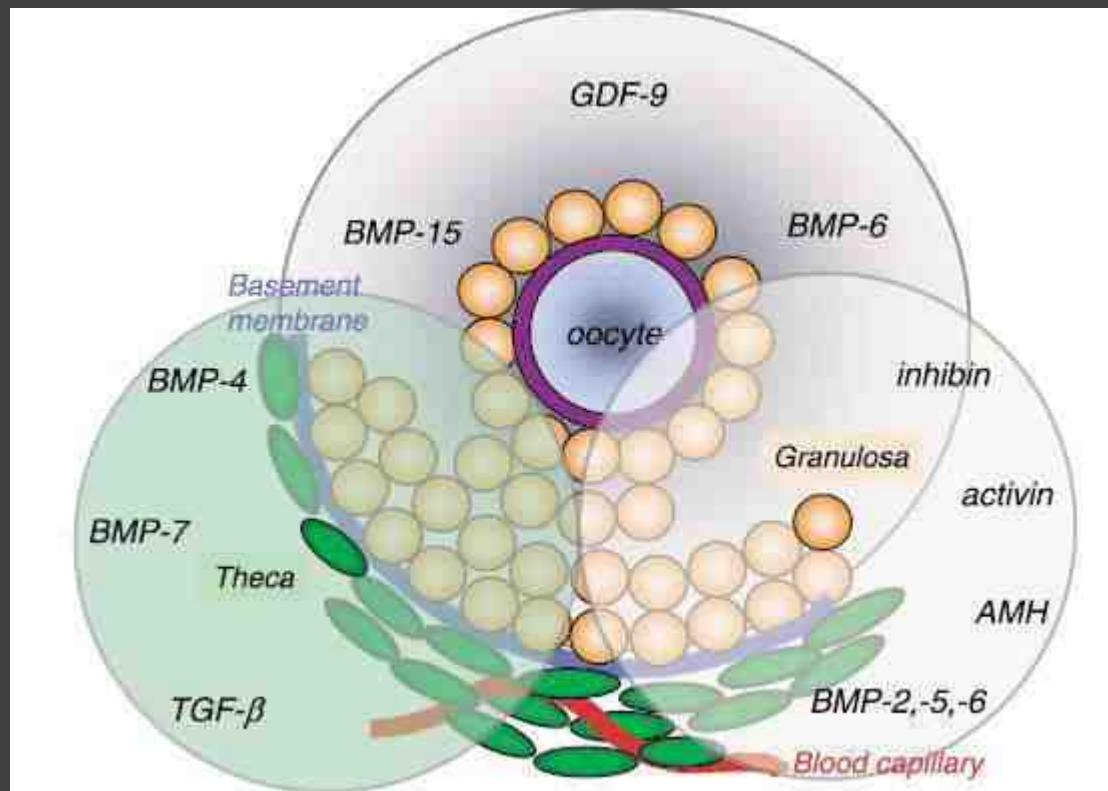
- AMH
- Foxo3a (forkhead transcription factor)
- Foxl2
- p27<sup>kip1</sup>
- Östrojen
- PTEN

# PARAKRİN MODULATÖRLER



LIGAND (main source)	Gonadotrophin-independent		Gonadotrophin-responsive	
	PRIMORDIAL	PRIMARY TO PRE-ANTRAL	ANTRAL	CORPUS LUTEUM
AMH [GC from primary to early antral stage]	From GC of growing preantral follicles ↓ Primordial follicle recruitment	↓ GC mitosis and FSH-responsive follicle progression??	*	*
BMP-4 BMP-7 [theca, TC]	From stromal theca: ↑ Primordial follicle activation	↑ GC proliferation, preantral follicle growth and follicle survival	↑ Basal and/or FSH-induced E2, inhibits activin production and ↑ GC proliferation; ↓ PA production by GC; ↓ Basal and LH-induced androgen production by TC	↓ GC luteinization / atresia; May ↓ ovulation
GDF-9 [oocyte from primordial / primary stage]	? Possible role in ↑ primordial follicle formation (sheep)	↑ Follicle progression beyond primary stage (essential)	↑ GC proliferation and ↓ PA production; ↑ Cumulus expansion; may regulate FSH-responsiveness of GCs and influence ovulation rate (sheep)	+
BMP-15 [oocyte from primordial / primary stage]	?	↑ Follicle progression beyond primary stage (essential in sheep, but not rodent)	↑ GC proliferation and ↓ PA production; may regulate FSH-responsiveness of GCs and influence ovulation rate (sheep)	*
BMP-6 [oocyte, GC from primordial / primary stage]	?	*	↑ GC proliferation; ↓ PA production by GC; ↑ TC androgen production	↓ GC luteinization / atresia
TGF-β [TC, GC, oocyte]	↑	↑ Conflicting data	↓ basal and LH-dependent androgen production by TC; conflicting data for GC	May mediate hematrophic action of progesterone (m); ↑ inhibitory activin βB expression in granulosa-theca cells (human)
Activin [GC from late preantral stage]	?	↑ GC proliferation; ↑ FSHR and FSH-induced aromatase expression; ↓ LH-induced androgen production by TC	↑ GC proliferation; ↑ FSHR and FSH-induced aromatase expression; ↓ LH-induced androgen production by TC; ↑ oocyte maturation	↓ GC luteinization / atresia; ↓ basal PA production
Inhibin [GC of antral follicles]	?	+	↑ LH-induced androgen production by TC; may ↓ growth of subdominant follicles	May ↑ basal PA production (human / primate only)

# PARAKRİN MODULATÖRLER



# NORMAL FOLİKÜLOGENEZİS-II



- DÜZENLENMİŞ BÜYÜME-SIKLIK SEÇİLME
  - LUTEO-FOLLİKÜLER GEÇİŞTEKİ SELEKTİF FSH ARTIŞI
  - FOLLİKÜL SEÇİMİ İÇİN POTENT STİMULUS
  - AMH(NEGATİF KONTROL)





# NORMAL FOLİKÜLOGENEZİS-III

- ERKEN FARKLILAŞMA
  - GRANÜLOZA HÜCRESİ İNHİBİN SALGILAMAYA BAŞLAMASI
  - FSH BAĞIMLI CEVAP
  - OVARIAN AKTİVİTE İZLENEBİLİR HALE GELİR
  - İNHİBİN B ↑
  - E2 VE İNHİBİN ETKİSİ İLE FSH PENCERESİ ÜÇÜNCÜ PERDENİN SONUNDA KAPANIR(MİD-FOLLİKÜLER FAZ)
  - LOKAL İNHİBİTÖR FAKTÖRLER+DÜŞÜK FSH KALAN KOHORTUN NEGATİF SELEKSİYONUNDA ROL OYNAR

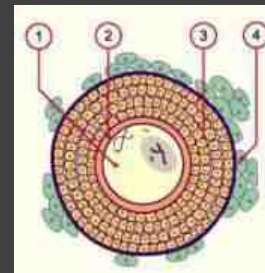
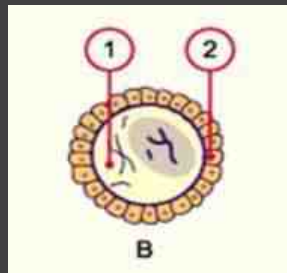
# PRIMER-PREANTRAL FOLLIKÜL

Aktivatörler

Inhibitörler

- TGF- $\beta$
- GDF-9
- Aktivinler
- BMP

- AMH

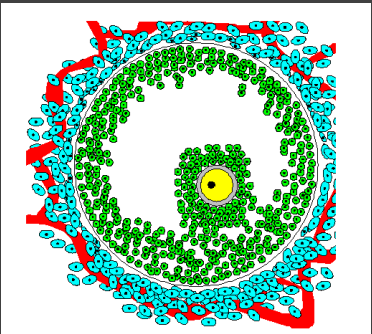


# NORMAL FOLİKÜLOGENEZİS-IV



## ■ TERMİNAL MATURASYON

- DOMİNANT FOLLİKÜL BÜYÜMEYE DEVAM EDER
- GEBELİK OLUŞMAZSA LUTEOLİZİS
- İNHİBİN A VE E2 AZALMASI SONUCU SIKLUS ARASI FSH YÜKSELMESİ İLE İKİNCİ SAHNE TEKRAR BAŞLAR
- BAŞLANGIÇ SEÇİLME VE BÜYÜME FAZİ SAHNE ARKASINDA ASİKLİK OLARAK DEVAM EDER



PRİMORDİAL FOLLİKÜL



KİT-LİGAND, bFGF

BÜYÜK PRİMER FOLLİKÜL



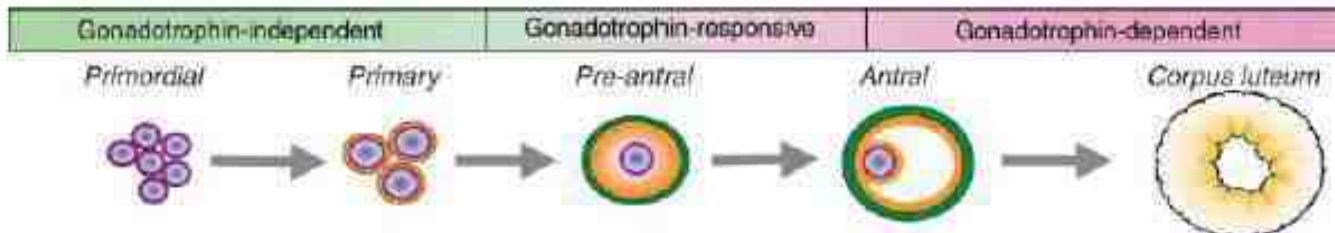
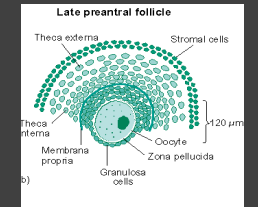
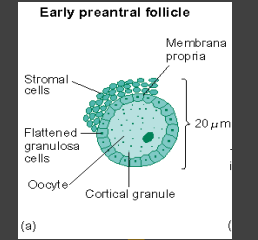
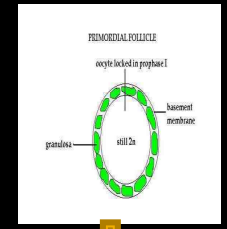
BİRKAÇ AY

PREANTRAL EVRE



~ +70 GÜN

MİD ANTRAL EVRE 2 MM



# CAST

- FSH
- LH
- E2
- P4
- AMH
- IGF-II
- IGFBP
- TGF
- NGF
- GDF-9
- FOLLISTATIN
- INHIBIN
- AKTIVIN
- BMP-5
- VGF
- SİTOKİN AİLESİ
- FAS LİGAND
- EGF
- FGF
- KIT
- LF
- LIF
- FOXO3A
- FOX12

# PCOS



- DOĞURGANLIK ÇAĞININ EN SIK ENDOKRİNOPATİSİ(>%5)
  - OLİGOANOVULASYON/MENSTRUEL BOZUKLUK
  - HİPERANDROJENİZM/HİRSUTİZMUS
  - METABOLİK BOZUKLUK/PERİFERİK HİPERİNSULİNEMİ
- SPESİFİK SANTRAL VEYA LOKAL DEFekten ZİYADE FONKSİYONEL BOZUKLUK SONUCU OLUŞUR

# PCOS PATOGENEZ

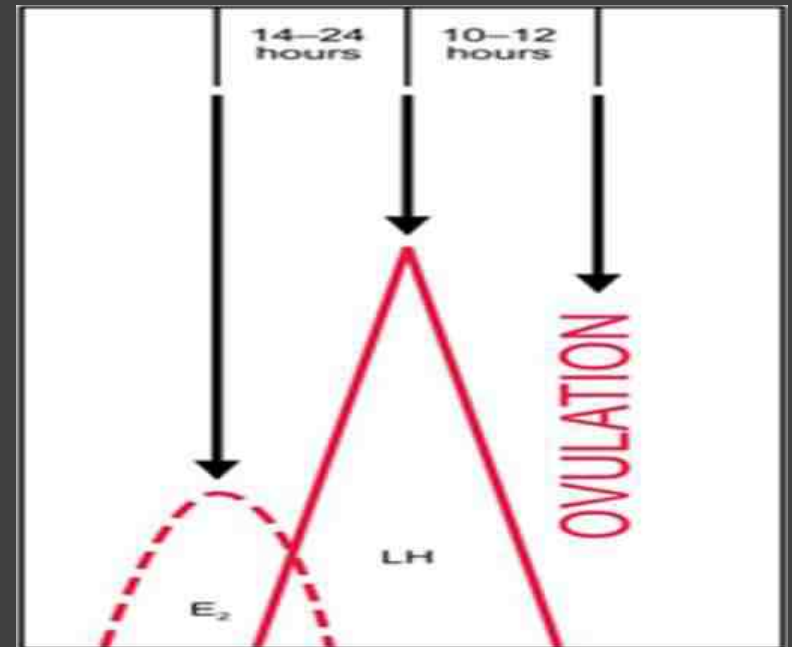
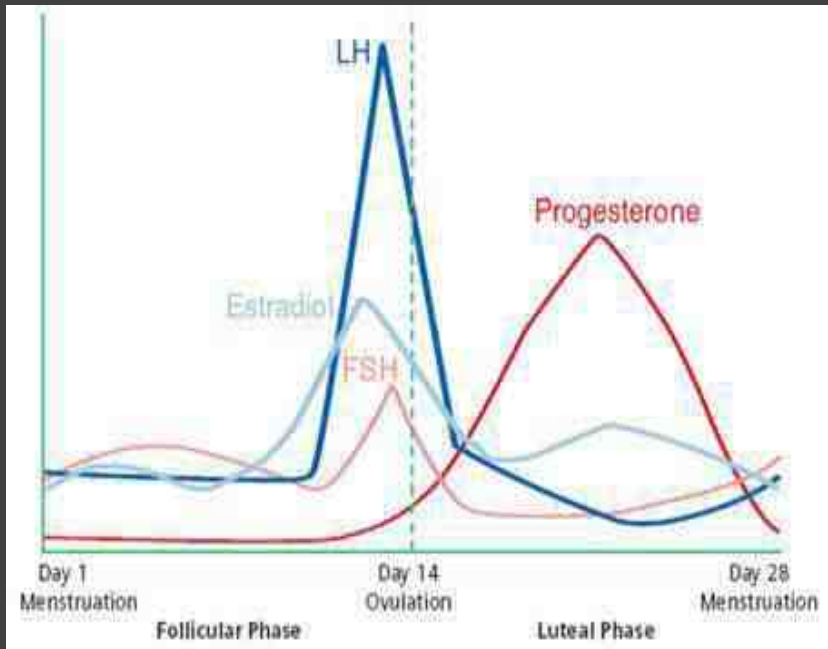
- RÖLATİF FSH YETMEZLİĞİ
- HİPERANDROJENİZM
- LH HİPERSEKRESYONU
- HİPERİNSULİNEMİ

# PCOS PATOGENEZİ

## DÜŞÜK FSH

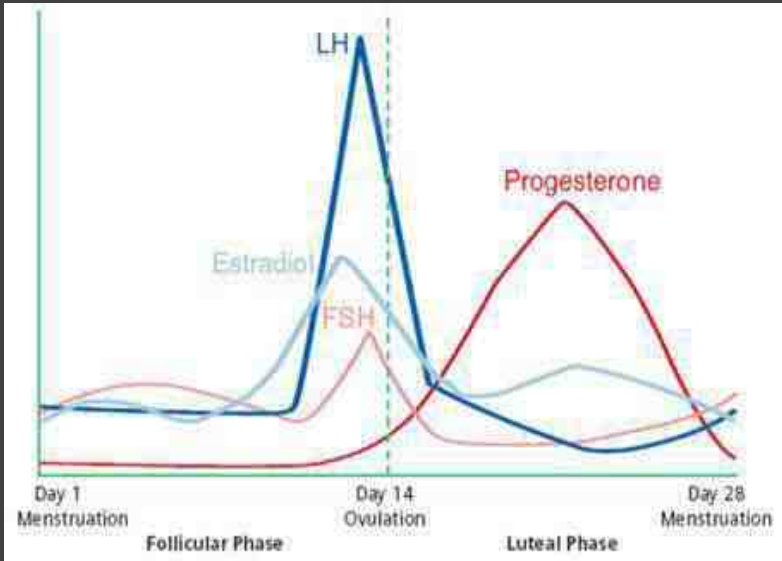
- GNRH PULSE ANORMALLİKLERİ
  - İNTRENSEK HİPOTALAMİK DİSFONKSİYON
  - ANORMAL FEEDBACK SİNYALLERİ
- ANDROJENLERİN PERİFERİK AROMATİZASYONU SONUCU OLUŞAN KRONİK ÖSTROJEN ARTIŞININ NEGATİF FEEDBACK ETKİSİ
- ARTMIŞ İNHİBİN B (KÜÇÜK FOLLİKÜLLERDEN)

# NORMAL OVULASYON

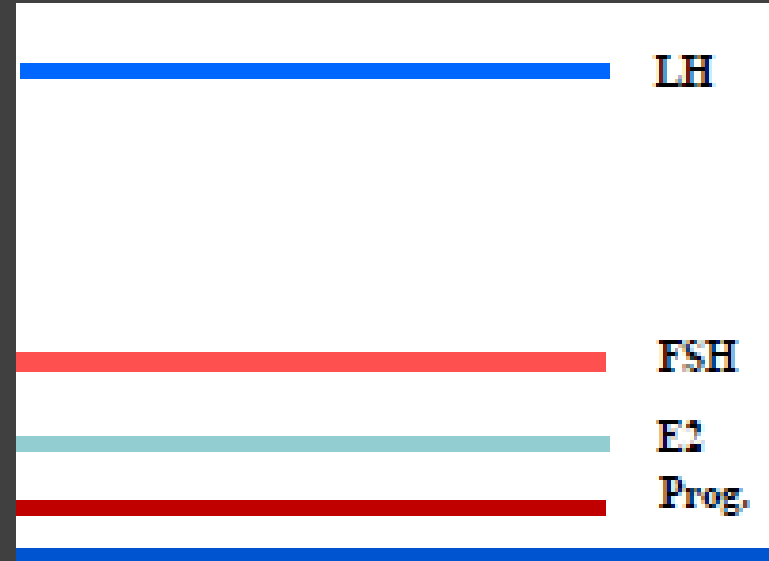


# PCOS PATOGENEZ RÖLATİF DÜŞÜK FSH

## OVULATUAR SIKLUS

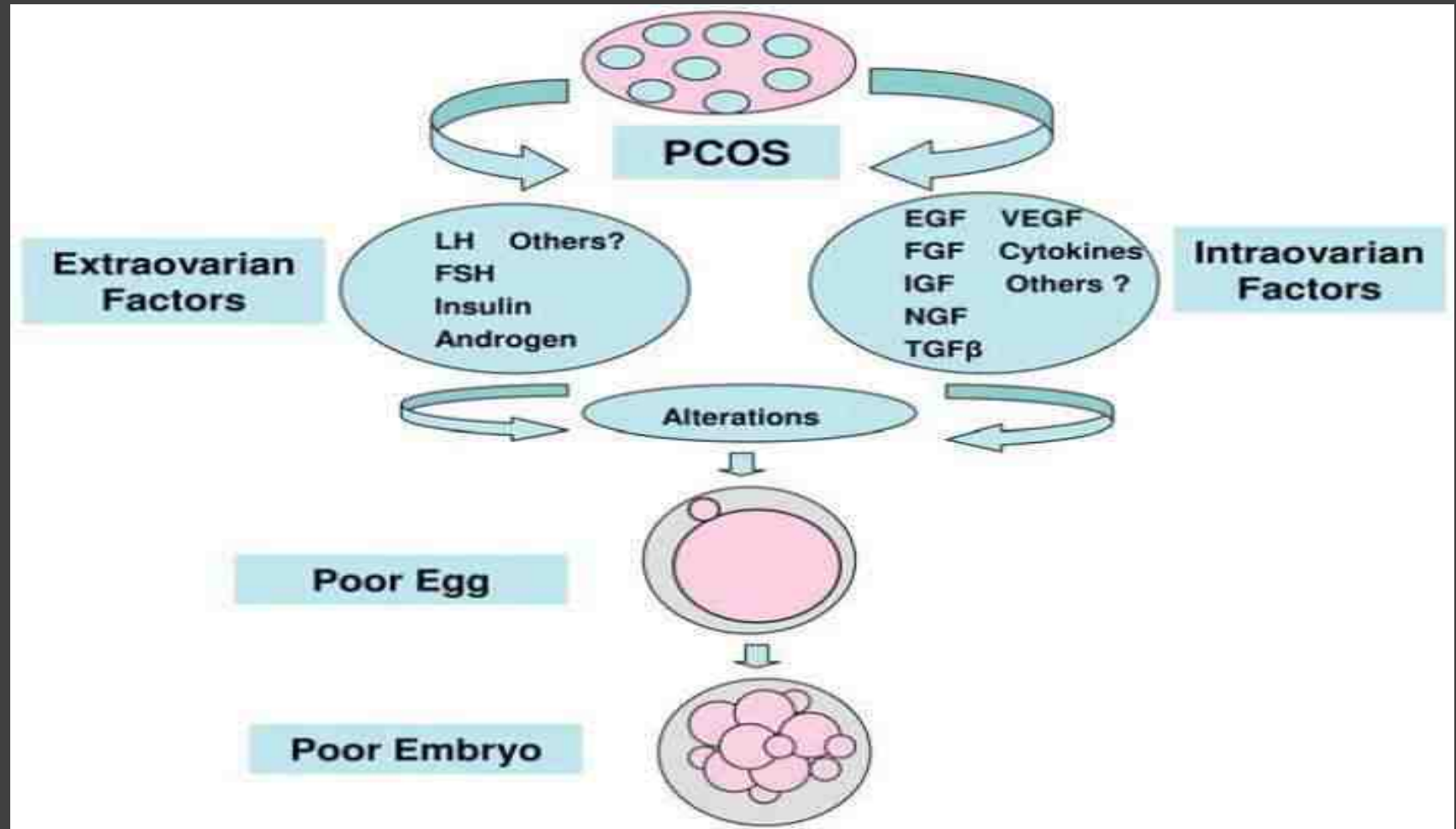


## PCOS



HORMONLARDA SIKLIK PATTERN YERINE SABIT DURUM

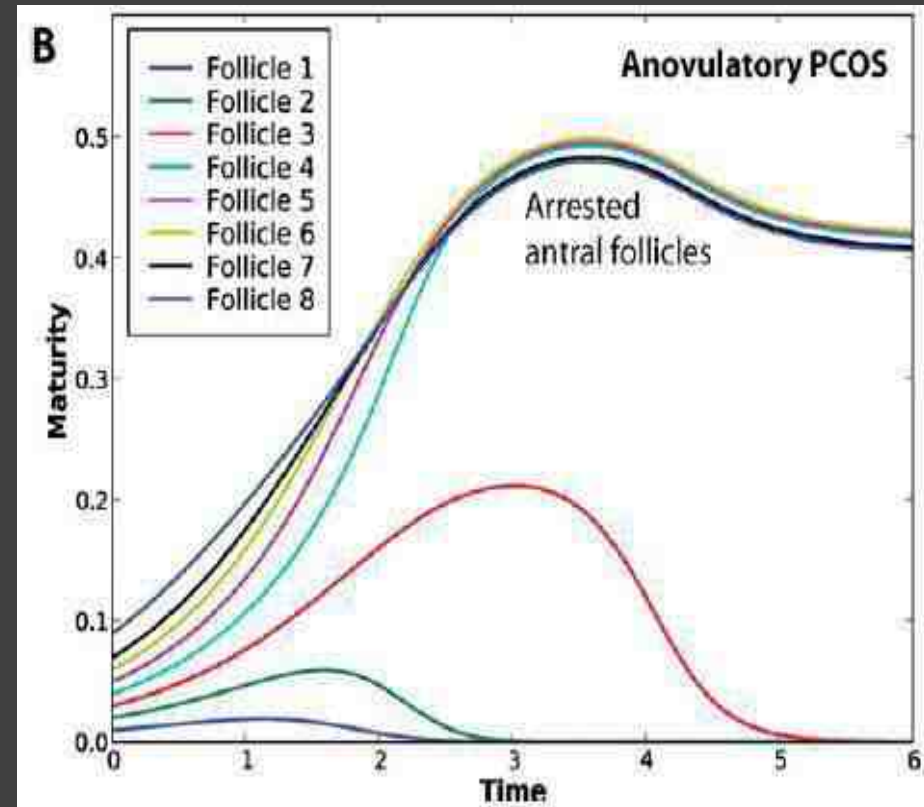
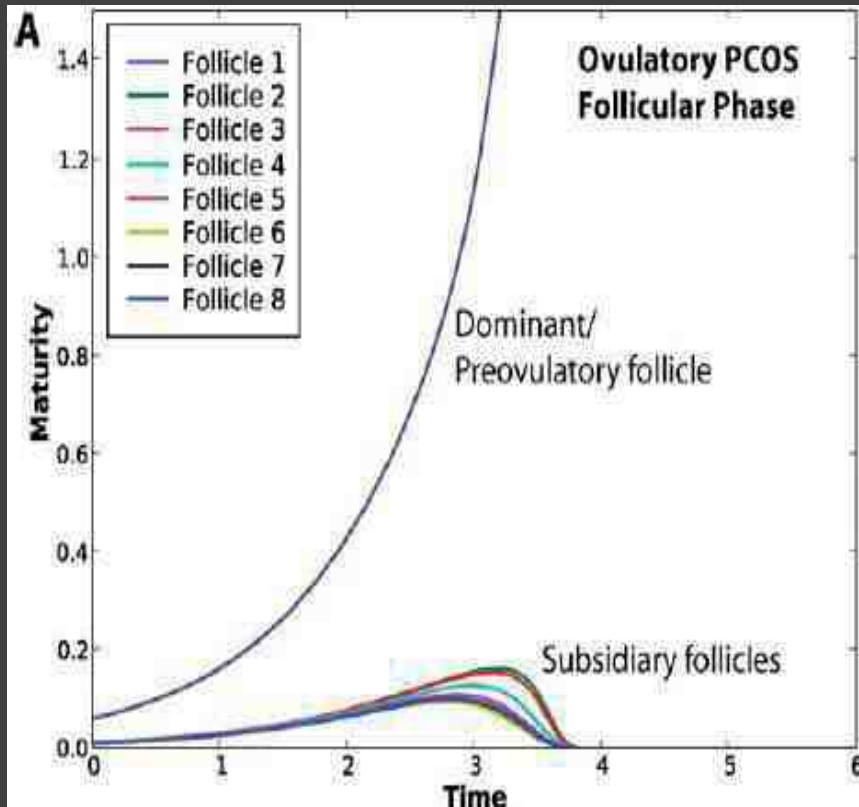
# PCOS & SUBFERTILITE



# PCOS-FOLLİKÜLER GELİŞİM

- ERKEN BÜYÜYEN VE SEÇİLEBİLİR FOLLİKÜL SAYISINDA ARTIŞ(İNTRAOVARIAN HİPRANDROJENİZM?)
- DOMİNANT FOLLİKÜL SEÇİM BOZUKLUĞU, BÜYÜK ANTRAL (5-8 MM) FOLLİKÜLLERDE GELİŞİM BOZUKLUĞU(FOLLİKÜLER ARREST)
  - SERUM FSH DÜZEYLERİ ERKEN FOLLİKÜLER FAZDA YETERLİ FOLLİKÜL GELİŞİMİNİ İNDÜKLEYECEK EŞİK DEĞERİN ALTINDA
    - ARTMIŞ TEKAL STEROİDOGENEZ AKTİVİTESİ
    - "PREANTRAL FOLLİKÜL GELİŞİMİNİN EN ERKEN BASAMAKLARINDA ANORMALLİK"

# FOLLİKÜLER GELİŞİM LACKER MODELİ

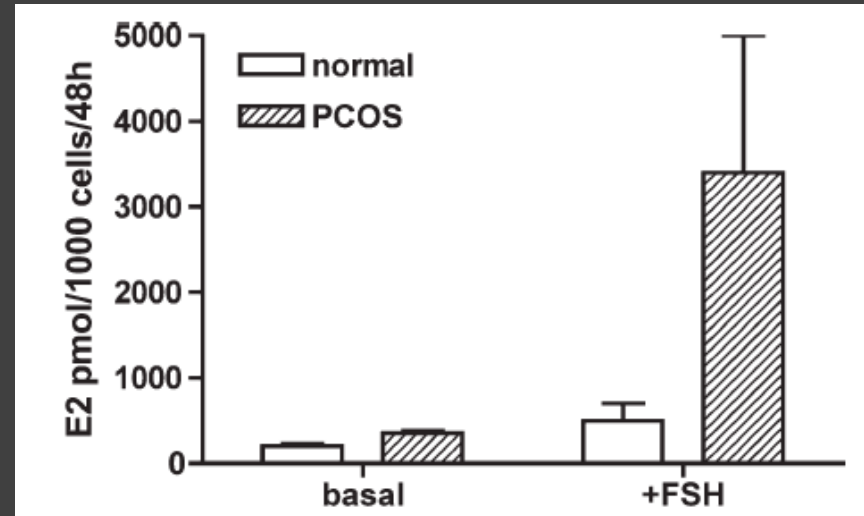


CHAVEZ, 1997

# PCOS-FOLLİKÜLER GELİŞİM

- KÜÇÜK ANTRAL FOLLİKÜLLERDE(2-4 MM) EKZOGEN FSH' A ARTMIŞ E2 VE P CEVABI
- BİR KISIM KÜÇÜK ANTRAL FOLLİKÜLLERDE UYGUNSUZ LH CEVABI
- BAZAL ARTMIŞ STEROİD ENZİM DÜZEYİ(E2)

## ANTRAL FOLLİKÜL-E2 CEVABI



MASON, 1994

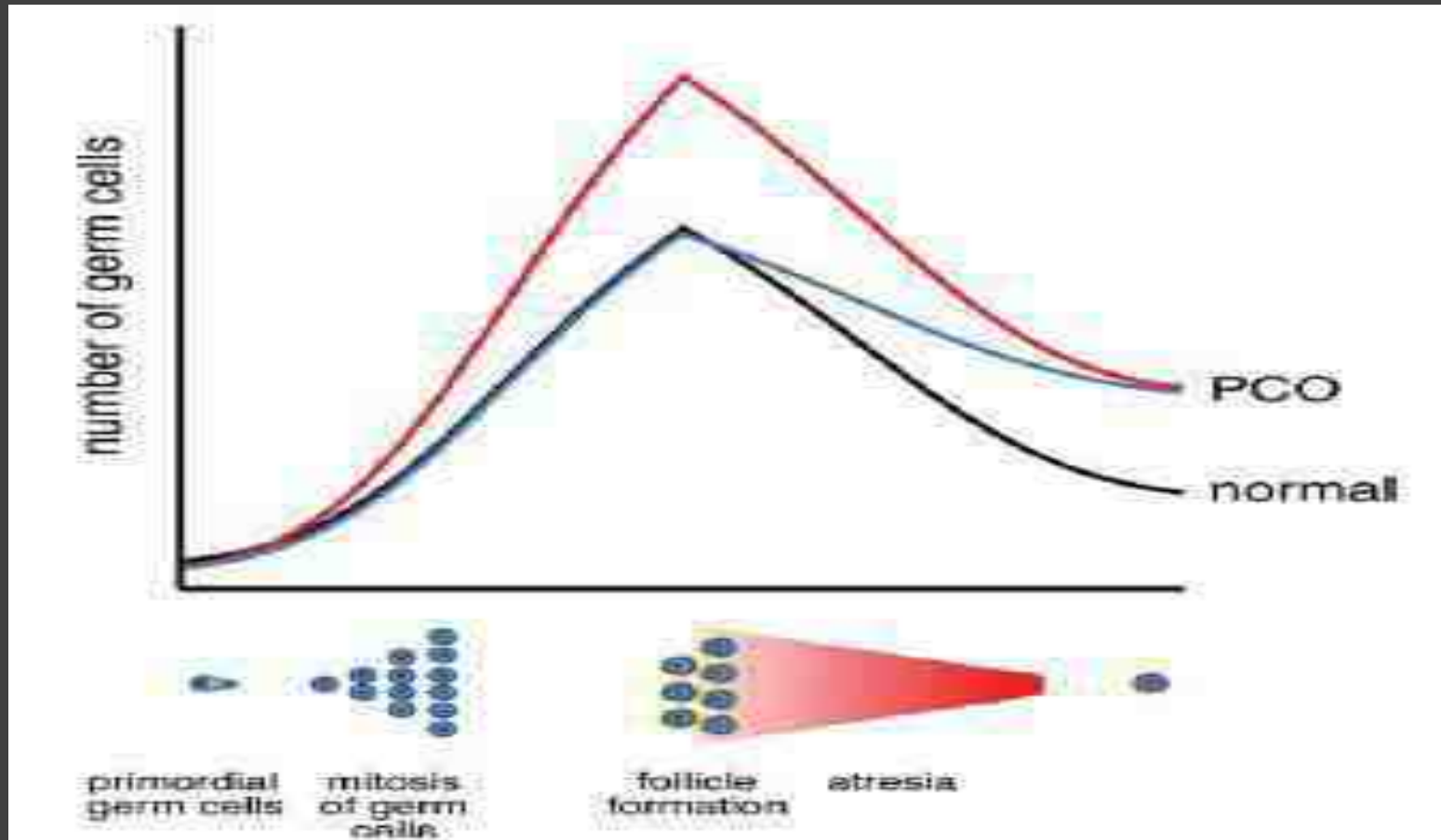
# PCOS-FOLLİKÜLER GELİŞİM

- GRANÜLOZA HÜCRELERİNDE PREMATÜR LH $\alpha$  EKSPRESYONU
- GRANÜLOZA HÜCRELERİNDE UYGUNSUZ TERMİNAL FARKLILAŞMA
- FSH BAĞIMSIZ DÖNEMLERDE ANORMAL PREANTRAL FOLLİKÜL GELİŞİMİ
- ANORMAL OOSİT GRANÜLOZA HÜCRE ETKİLEŞİMİ

# PCOS-FOLLİKÜL GELİŞİMİ

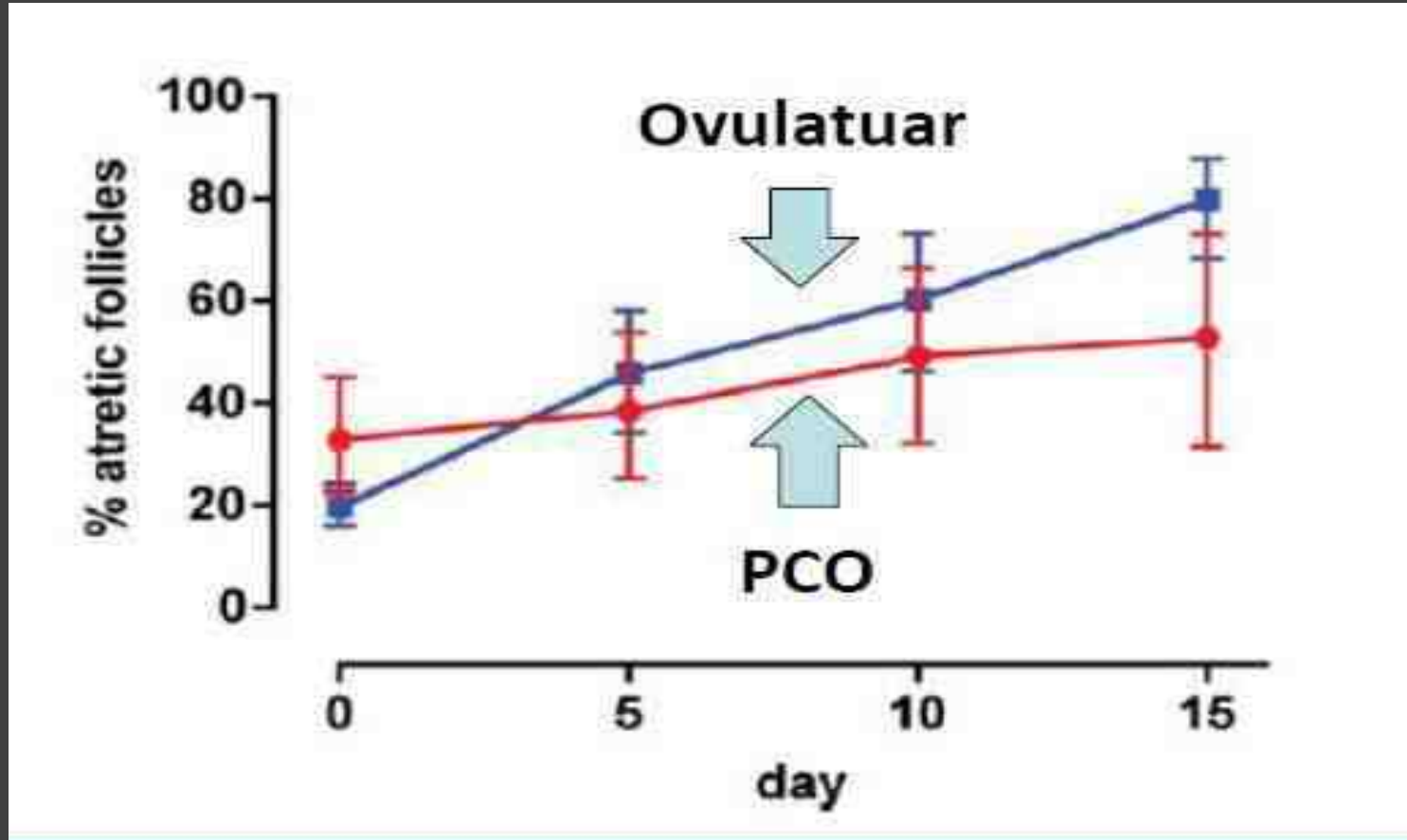
- ARTMIŞ PRIMORDIAL FOLLİKÜL SAYISI
  - FETAL OVERLERDE ARTMIŞ PRIMORDIAL GERM HÜCRELERİ
  - GERM HÜCRE/GRANÜLOZA HÜCRELERİNDE ARTMIŞ MITOZ
  - AZALMIŞ FOLLİKÜL APOPTOZİSİ

# PCOS-PREANTRAL FOLLİKÜL YOĞUNLUĞU GERM HÜCRE MITOZ VE ATREZİSİ-İNTRAUTERİN

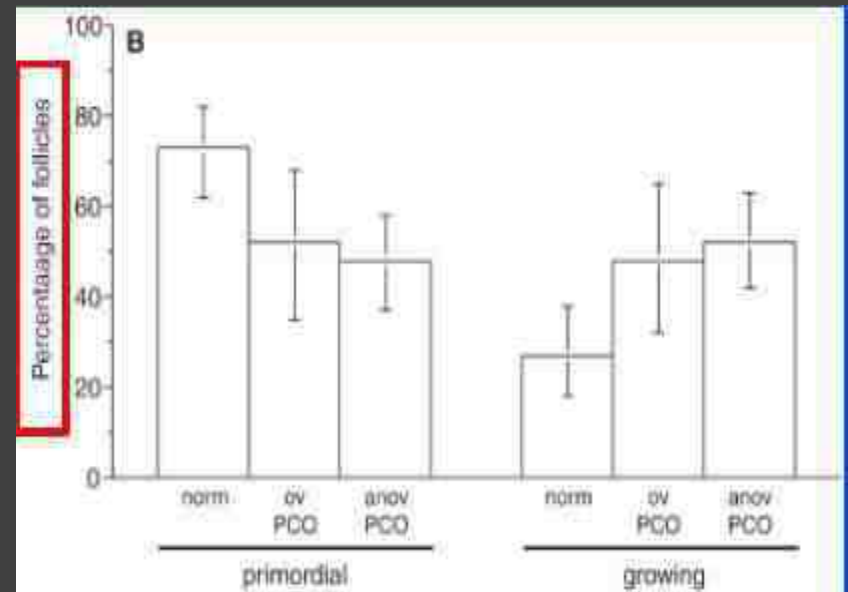
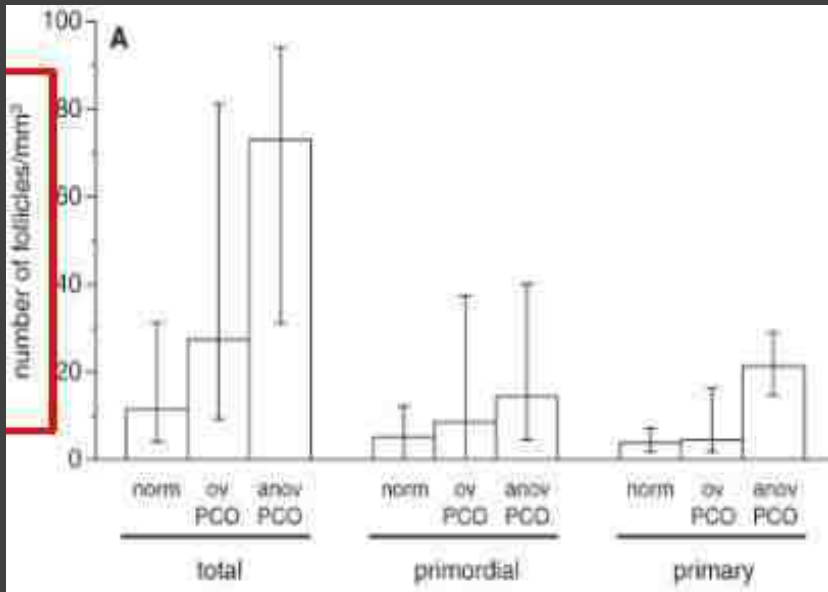


WEBBER, 2003

# AZALMIŞ PREANTRAL FOLLİKÜL ATREZİSİ KÜLTÜRDE ARTMIŞ SAĞKALIM

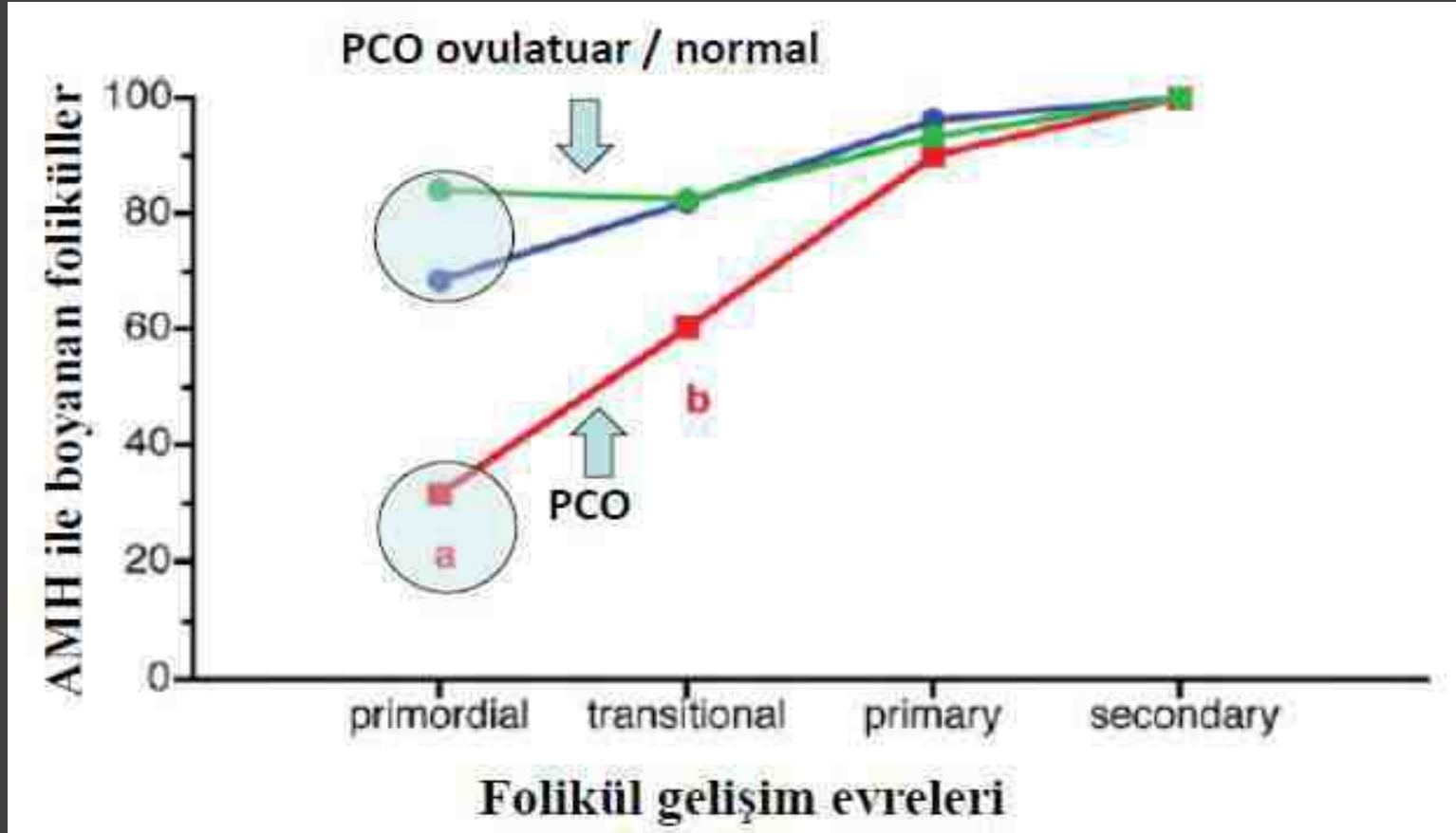


# PCOS-REZERV FOLLIKÜL



WEBBER, 2007

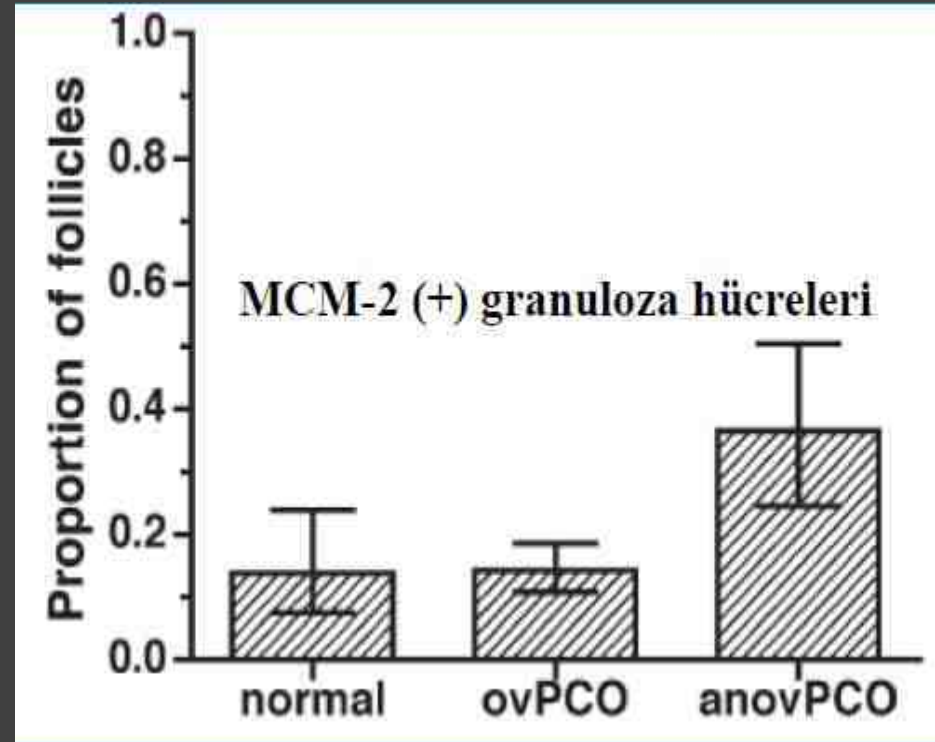
# PCOS-BÜYÜYEN FOLLİKÜL AMH' NİN ROLÜ



# PCOS

## ARTMIŞ GRANÜLOZA HÜCRE MİTOZU

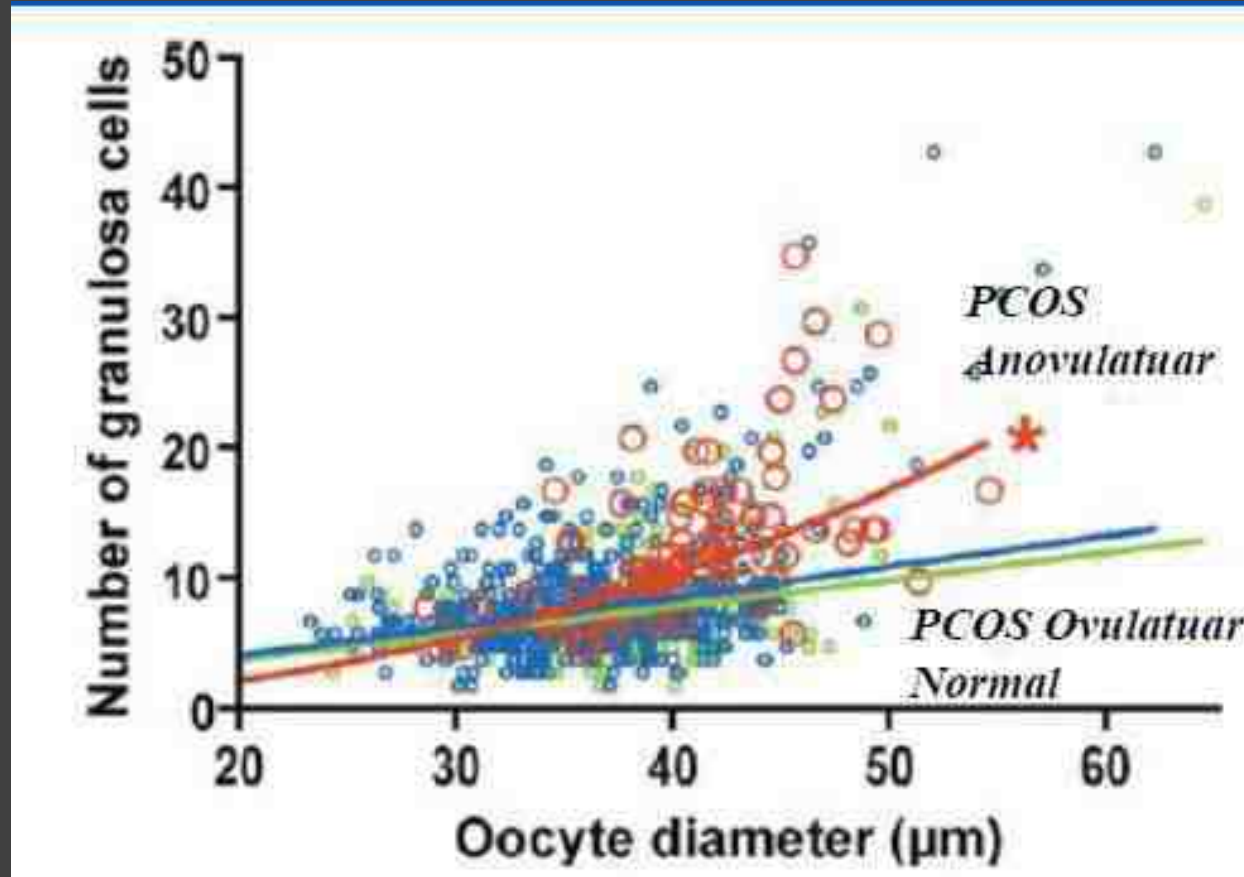
- ARTMIŞ GRANÜLOZA HÜCRE MİTOZU
- MCM-II (MINI CHROMOSOME MAINTENANCE PROTEIN) GRANÜLOZA HÜCRE BÖLÜNMESİ
- PCOS' LU HASTALARDA PRIMORDIAL FOLLİKÜLLERDEN ERKEN ANTRAL FOLLİKÜLLERE DOĞRU MCM- 2 EKSPRESYONU ARTMAKTA



STUBBS, 2007

# PCOS

## ABERRAN GRANÜLOZA-OOSİT ETKİLEŞİMİ



STUBBS, 2007

# PCOS FOLLİKÜL DİNAMİĞİ SONUÇLAR

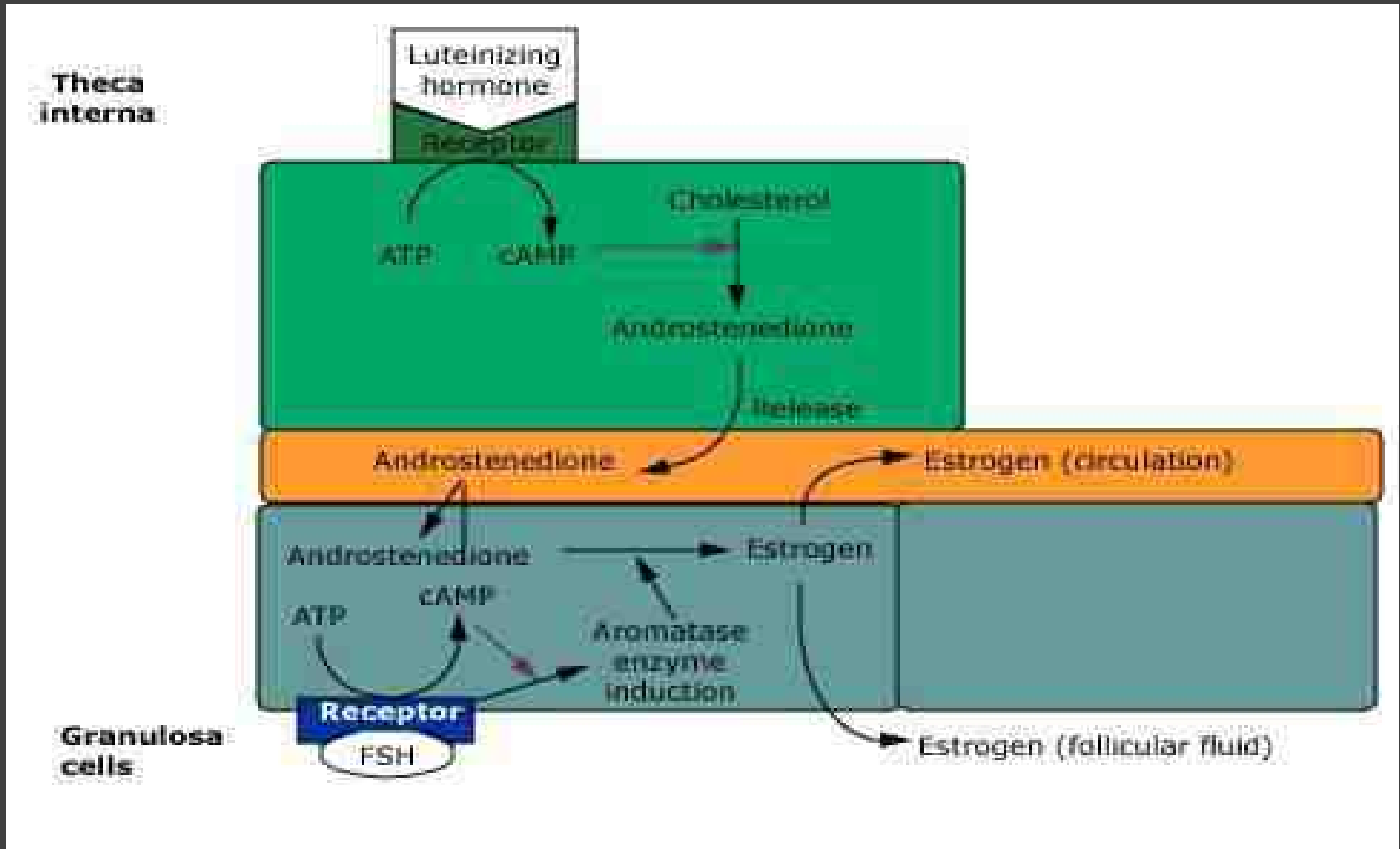
- GONADOTROPİNLERDEN BAĞIMSIZ FOLLİKÜLOGENEZİSİN ERKEN EVRELERİNDE DEFEKT
- ARTMIŞ SEÇİLEBİLİR FOLLİKÜL YOĞUNLUĞU
- BİR GRUP FOLLİKÜLDE ARTMIŞ FSH VE LH SENSİTİVİTESİ
- FOLLİKÜLER ARREST: BU AŞIRI DUYARLI FOLLİKÜLLER ERKEN MATÜR OLUR, YÜKSEK E2 SALGILAR, FSH SUPRESE OLUR. SUPRESE FSH İLERİ FOLLİKÜL GELİŞİMİ İÇİN YETERLİ OLMAZ
- ABERRAN OOSİT-GRANÜLOZA HÜCRE FONKSİYONLARI
- OOSİT GEN EKSPRESYON DEFEKTLERİ?



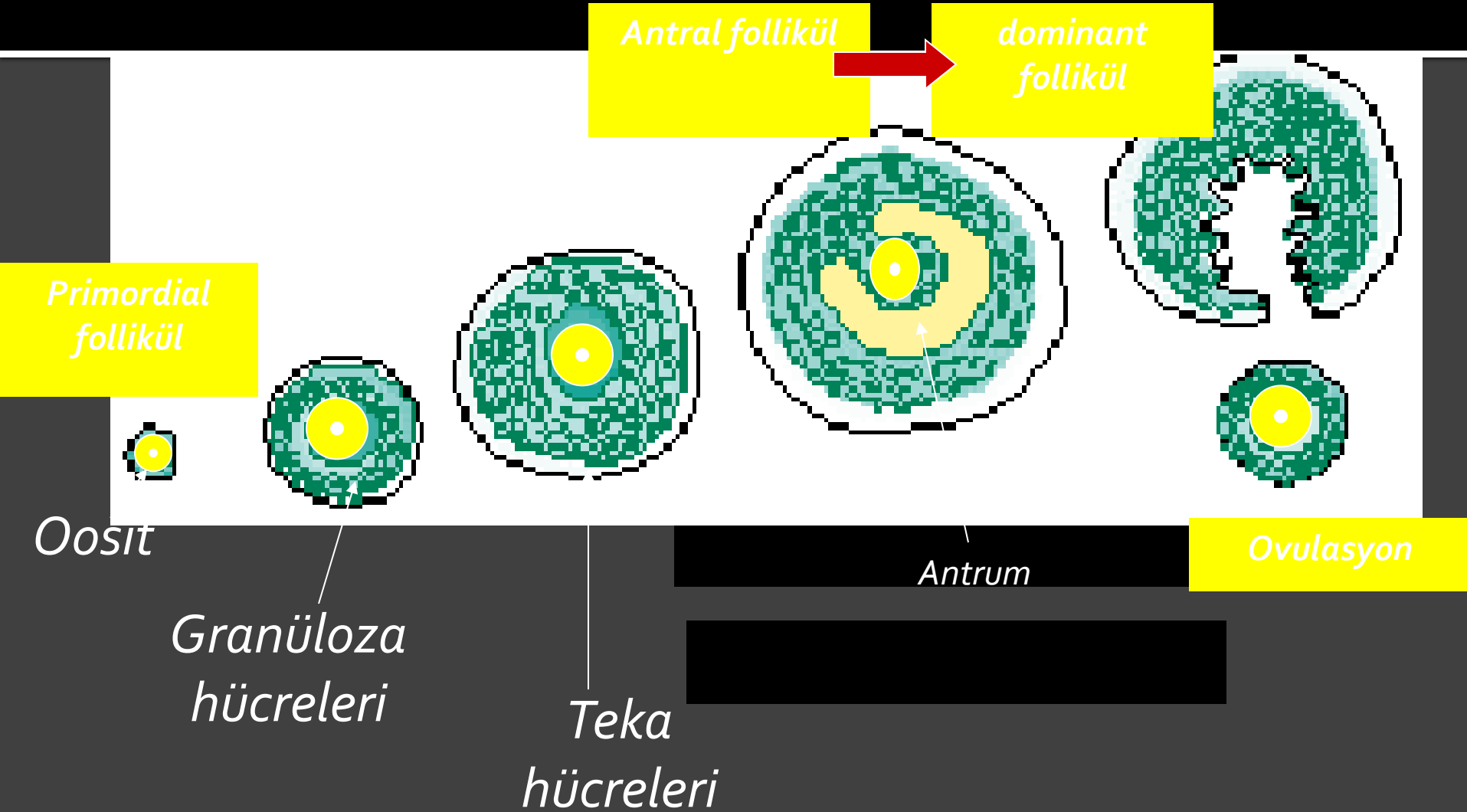
**TEŞEKKÜRLER...**

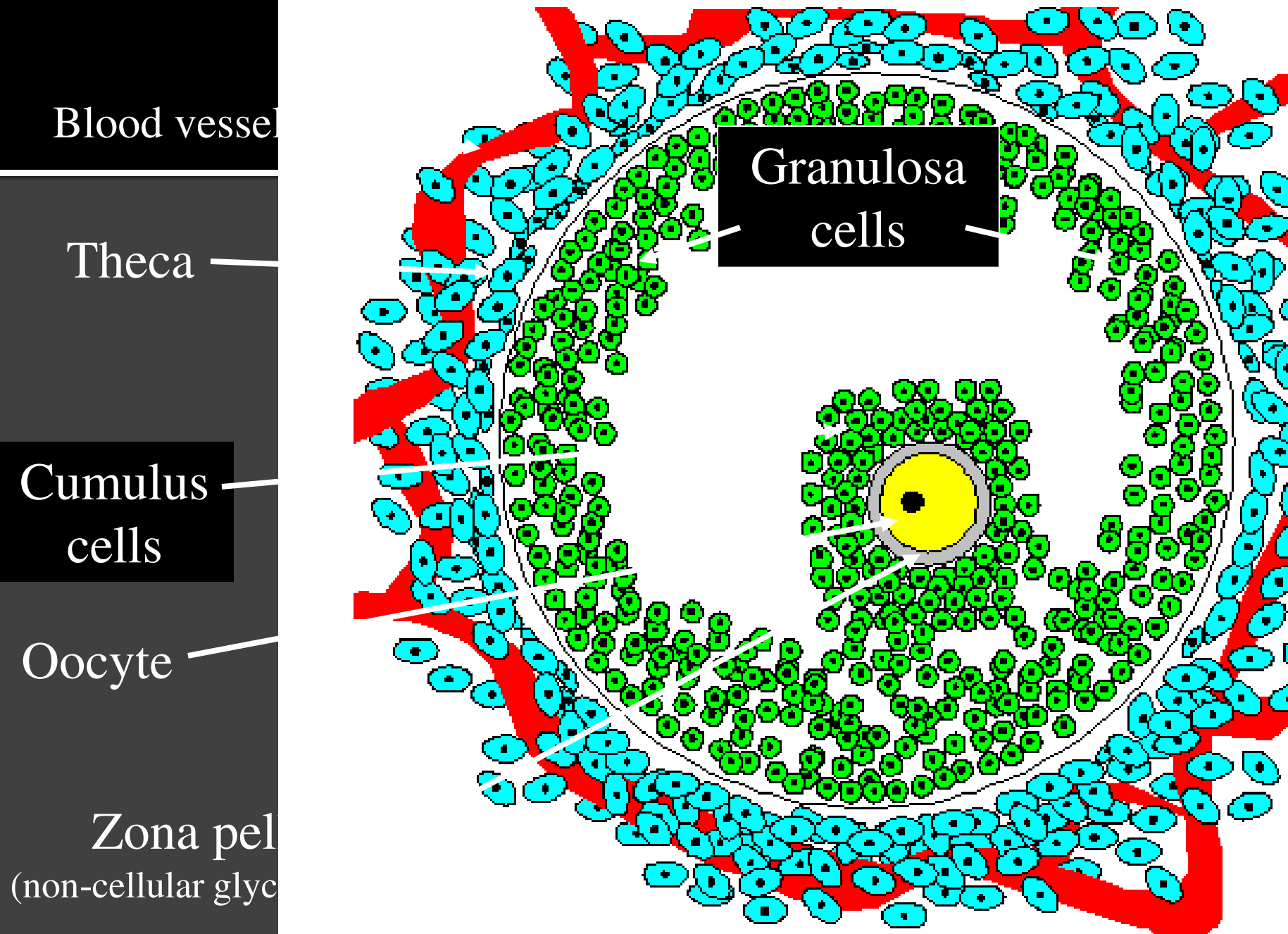


# İKİ HÜCRE İKİ GONADOTROPİN TEORİSİ



# Foliküllerin büyümesi





# FOLLİKÜLER GELİŞİM: Androjenler

