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BSc in Reproductive and Developmental Biology

Folliculogenesis

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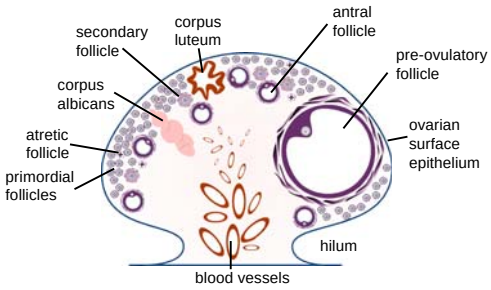
Institute of Reproductive and Developmental Biology

Follicles contain oocytes and populate the ovary



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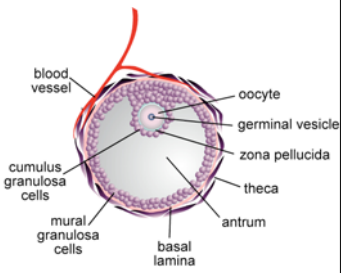
Function of a follicle

- Produce steroid hormones
- Create a specialized environment to nourish and mature a healthy oocyte*



* see lecture on "oocyte maturation and meiosis"

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Folliculogenesis

- Follicle formation before/around time of birth
- Initiation of follicle growth
- Follicle and oocyte growth
- Antrum formation
- Selection of growing antral follicles
- Selection of dominant follicle
- Ovulation
- Corpus luteum formation

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Ovary contains 'pool' of arrested oocytes, enclosed in follicles

- Female born with complete supply of oocytes
- **All** oocytes are arrested in prophase of Meiosis I, except the ovulating oocyte
- Most follicles in cortex are arrested at primordial and primary stages
- Some follicles towards medulla are at later stages
- Throughout reproductive life, a small proportion of follicles escape arrest and start growing

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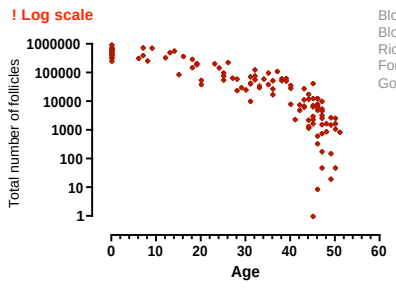
Declining number of oocytes



Block 1952
Block 1953
Richardson 1987
Forabosco 1991
Gougeon 1994

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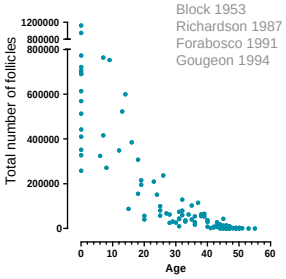
Declining number of oocytes

- Exponential decline in oocyte number
- Great variability in oocyte endowment at birth (~600,000)
- Only 10,000 oocytes remain in 20s
- 60-fold decline in first 20 years!

Decline:

- entry into growth phase
- atresia

! Linear scale



Block 1952
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Richardson 1987
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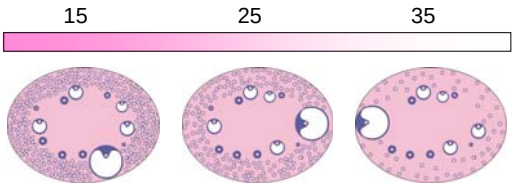
Primordial pool declines with age



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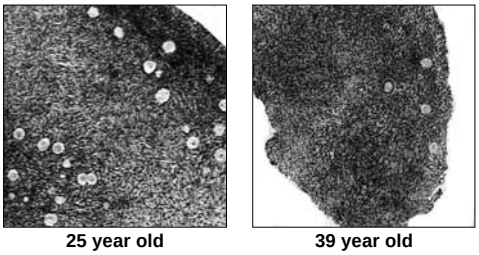
Follicles become more sparse with age



25 year old **39 year old**

histology of ovarian cortex

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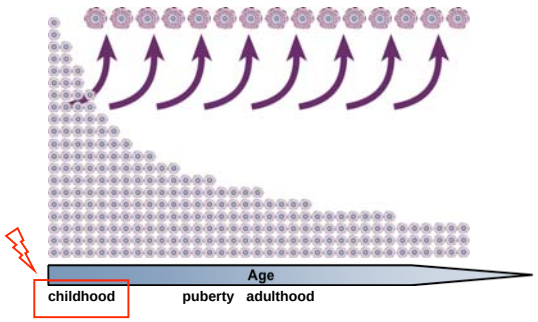
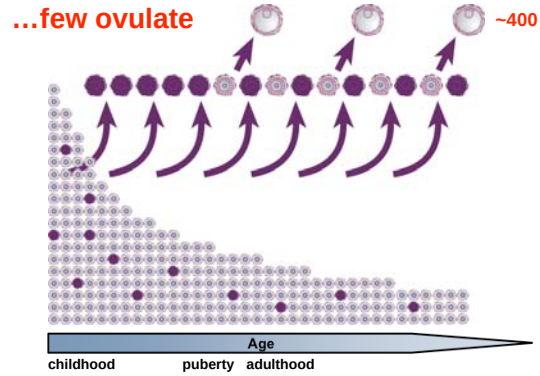
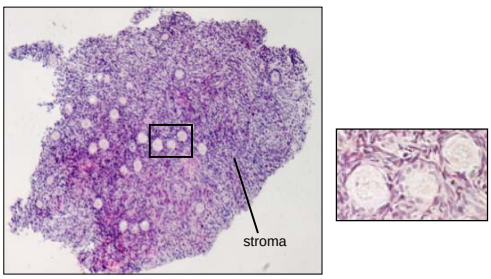
Follicles initiate growth all the time



…few ovulate



Human cortex contains preantral follicles



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What regulates initiation of growth?

Regulation

- Not known
- Release of inhibitory signal?
- Stimulatory signal?

Growth

- Granulosa cells become cuboidal and start dividing
- Oocyte starts to grow

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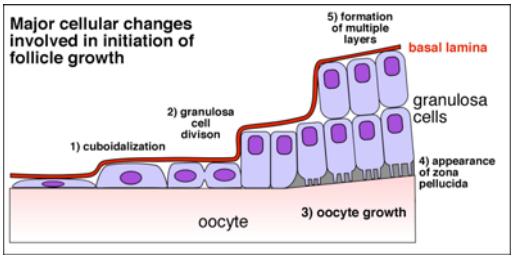
Cellular changes during initiation



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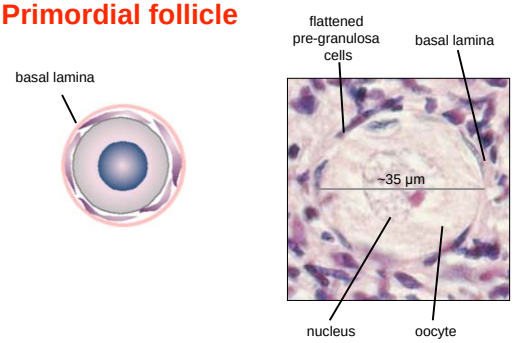
Primordial follicle



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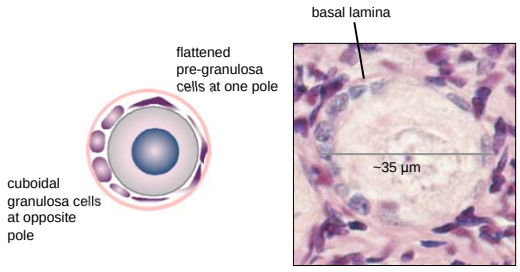
Transitional follicle



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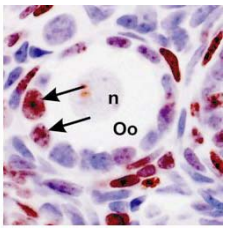
Granulosa cells start dividing

n= nucleus
Oo= oocyte



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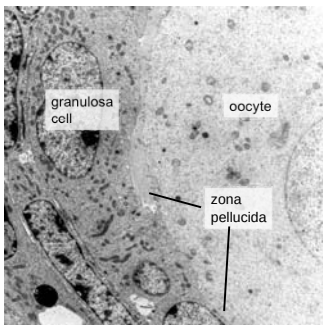
Synthesis of zona pellucida



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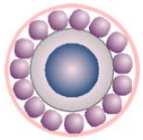
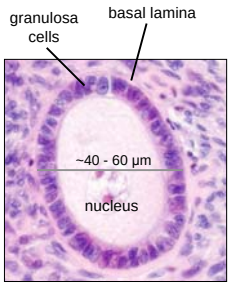
Primary follicle



- single layer of cuboidal granulosa cells
- oocyte starting to grow



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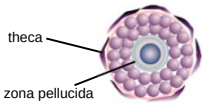
Secondary follicle

- double layer of cuboidal granulosa cells
- theca cells start to assemble
- zona pellucida around oocyte produced



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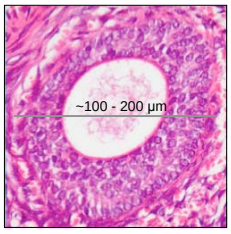
Preantral follicle

- multiple layers of granulosa cells
- continued oocyte growth



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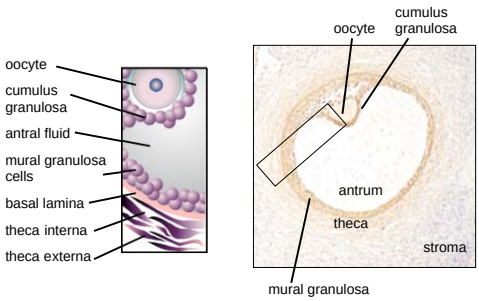
Antrum formation

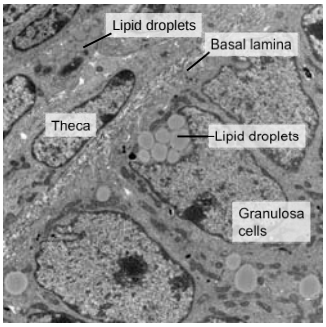
Antrum:

- Fluid-filled cavity
- Forms when follicle is ~200μm in diameter
- Occurs when ~2000 granulosa cells in all species
- Function
  - prevent necrosis in centre of follicle?

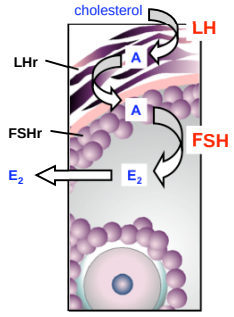
Antral follicle



TEM (mouse day 21 ovary)



Steroidogenic function of antral follicle



- Theca cells express LH receptors
- With LH stimulation, theca cells produce androgen
- Androgen enters granulosa cells
- Granulosa cells express FSH receptors.
- Under FSH stimulation, androgen converted to oestradiol

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Control of follicle growth

Intraovarian growth regulatory factors

- IGF-I
- Steroids
- TGFβ superfamily members
  - Growth differentiation factor-9 (GDF-9)
  - Bone Morphogenetic Proteins (BMPs)
  - Anti Müllerian hormone (AMH)
- Wnt/frizzled family

Endocrine factors

- FSH
- LH

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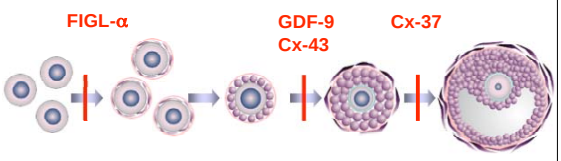
Regulation of folliculogenesis



FIGL-α: Factor in the germline-a
GDF-9: Growth differentiation factor-9
Cx-43: Connexin-43
Cx-37: Connexin-37

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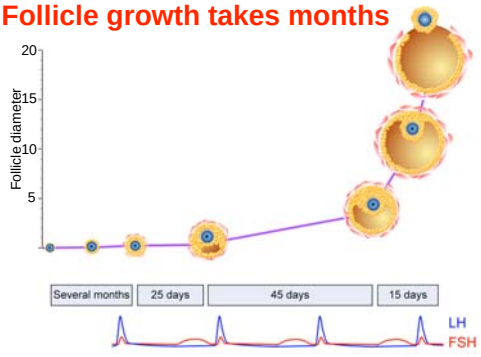
Follicle growth takes months



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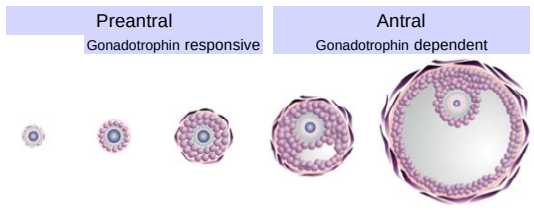
Human follicle development



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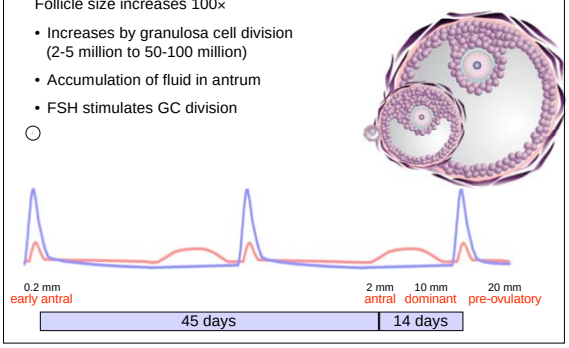
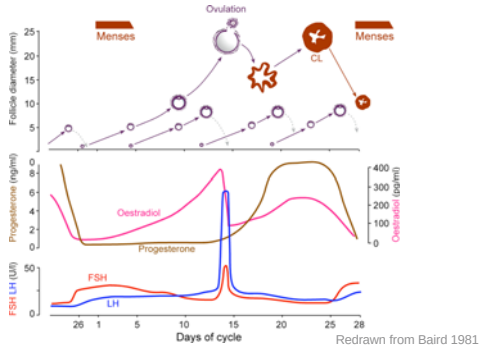
Antral follicle growth

Follicle size increases 100×

- Increases by granulosa cell division (2-5 million to 50-100 million)
- Accumulation of fluid in antrum
- FSH stimulates GC division



The ovulatory cycle



Redrawn from Baird 1981

The ovulatory cycle

Luteal phase

- Corpus luteum has a limited lifespan (14 days)
- As CL regresses, progesterone and oestradiol fall
- Fall in P and E_2 removes negative feedback on production of FSH and LH
- FSH levels start to rise……

Follicular phase

- ….Selection of next cohort of growing follicles

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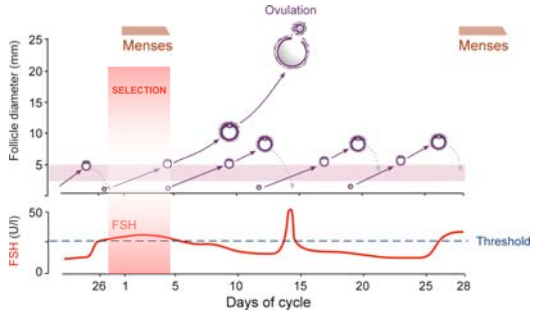
Follicle selection



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Follicle selection

- Throughout the cycle there are early antral follicles
- Without sufficient FSH, these die
- When FSH rises above a certain threshold, at the start of the cycle, follicles which are between 2 - 5 mm in diameter survive, and continue growing
- i.e. are selected
- 5 - 10 follicles are selected to grow
- FSH stimulates granulosa cell division

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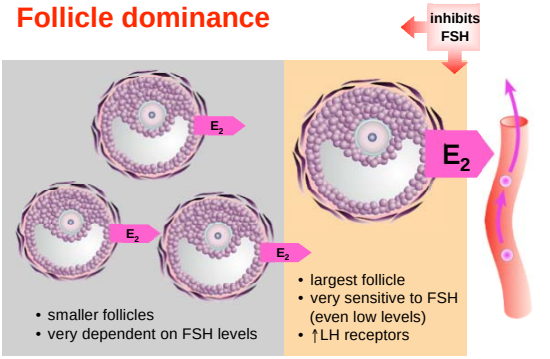
Follicle dominance



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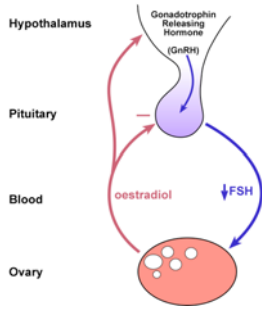
Increased E_2 inhibits FSH production



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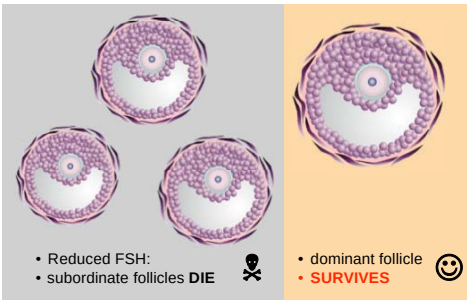
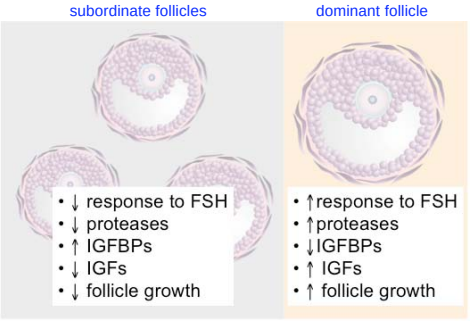
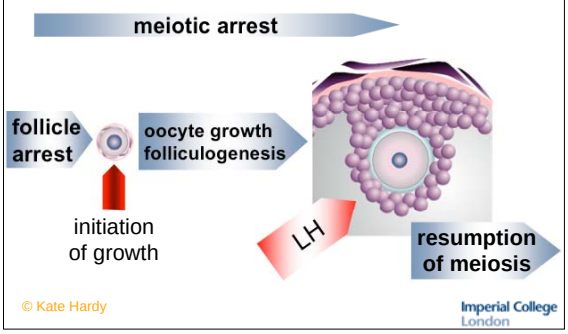
Follicle dominance (1 oocyte ovulated)



Amplification of FSH effect



Remember! Oocyte has been arrested throughout folliculogenesis, until…



LH surge stimulates

- ovulation
- luteinization (follicle)
- resumption of meiosis (oocyte)
- cumulus expansion
- LH surge stimulates expression of
  - prostaglandins
  - proteolytic enzymes

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Ovulation

- Rupture of ovarian surface to allow release of oocyte
  - activation of collagenase and proteases
- Reorganization and remodelling of follicle → corpus luteum
  - recruitment and invasion of leukocytes and macrophages
  - vascularization of follicle

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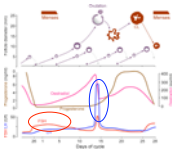
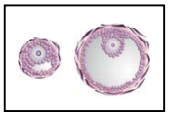
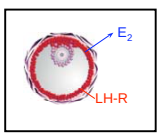


Proliferation



In selected follicles
FSH induces
FSH receptor
IGF-I production etc

Differentiation



FSH induces
Aromatase expression
(leads to ↑E_2)

LH receptor expression
in granulosa cells
(only in dominant follicle
≥ 10mm diameter)
(to enable response to LH surge)

Ovulation

LH surge induces
terminal GC differentiation
cumulus expansion
resumption of meiosis
THEN
ovulation
luteinization

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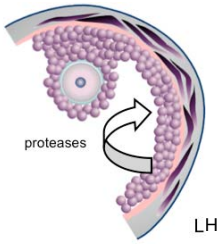
Follicle rupture



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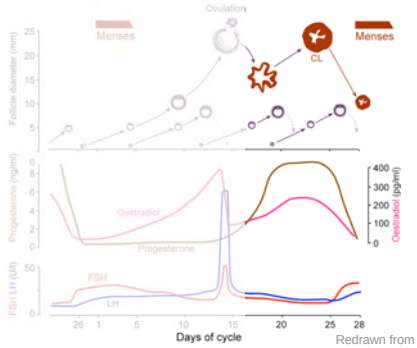
The luteal phase

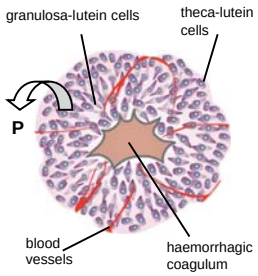


Redrawn from Baird 1981

Corpus luteum formation

After ovulation

- Granulosa and theca cells luteinize
- blood vessels invade granulosa-lutein cells
- increased vasculature supplies exogenous cholesterol for progesterone production



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Luteolysis

If no pregnancy

- Functional luteolysis
  - drop in progesterone production around day 22-24
  - allows development of new follicles
- Structural luteolysis
  - removal of corpus luteum
- Involution of the corpus luteum to form corpus albicans
  - CL invaded by connective tissue
  - scar of collagen
  - eventually resorbed

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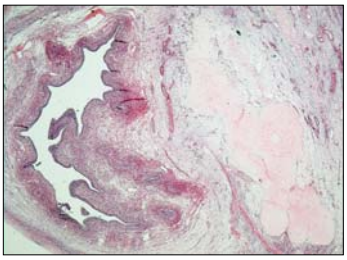
Corpus luteum and corpus albicans



corpus luteum corpus albicans

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