UNIL | Université de Lausanne
Faculté de biologie et de médecine

UNIVERSITÉ DE GENÈVE

The menstrual cycle

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Training Course in Reproductive Health Research – Geneva 2008

CHUV

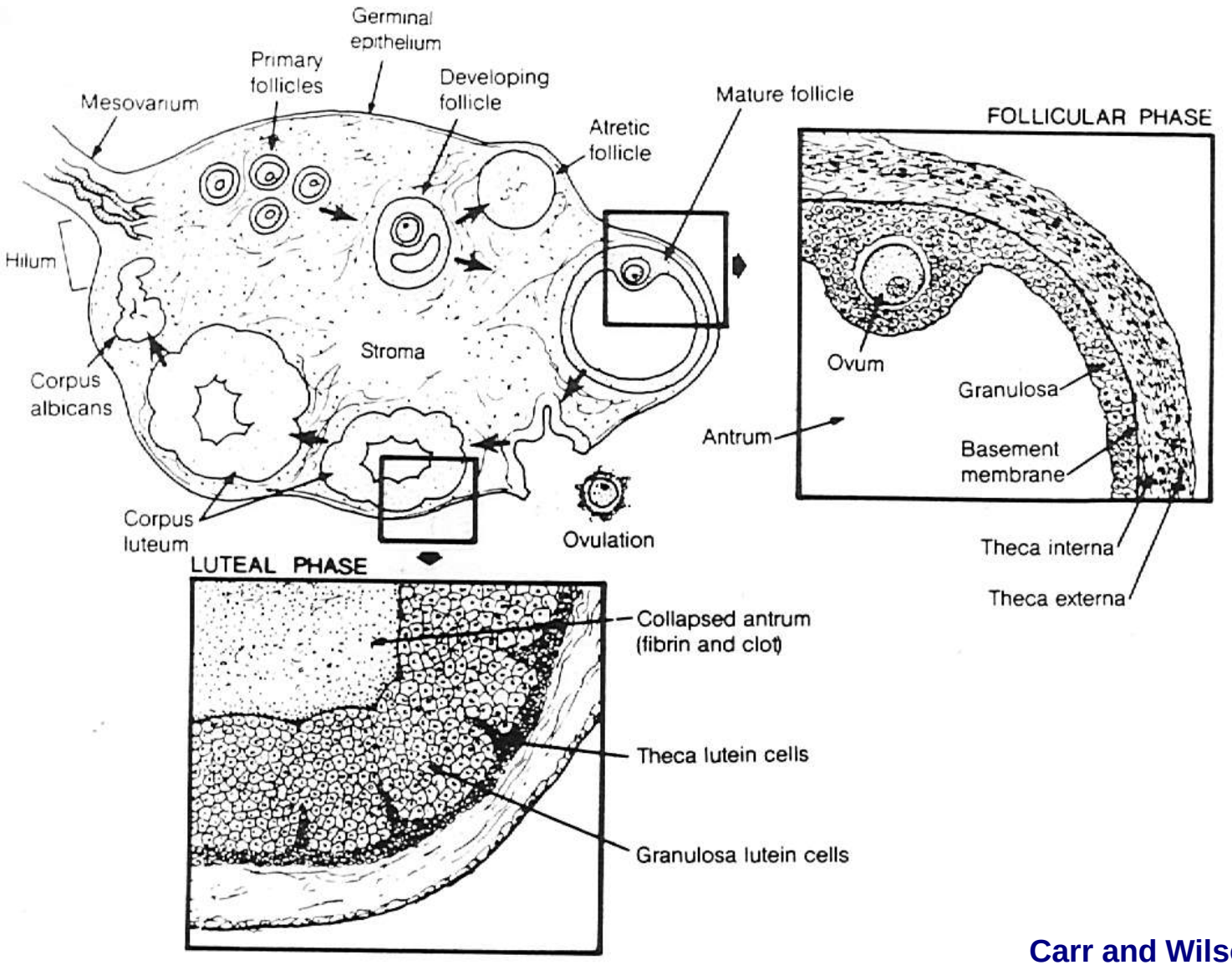
CardioMet

Two functions of the ovary

Gametogenesis

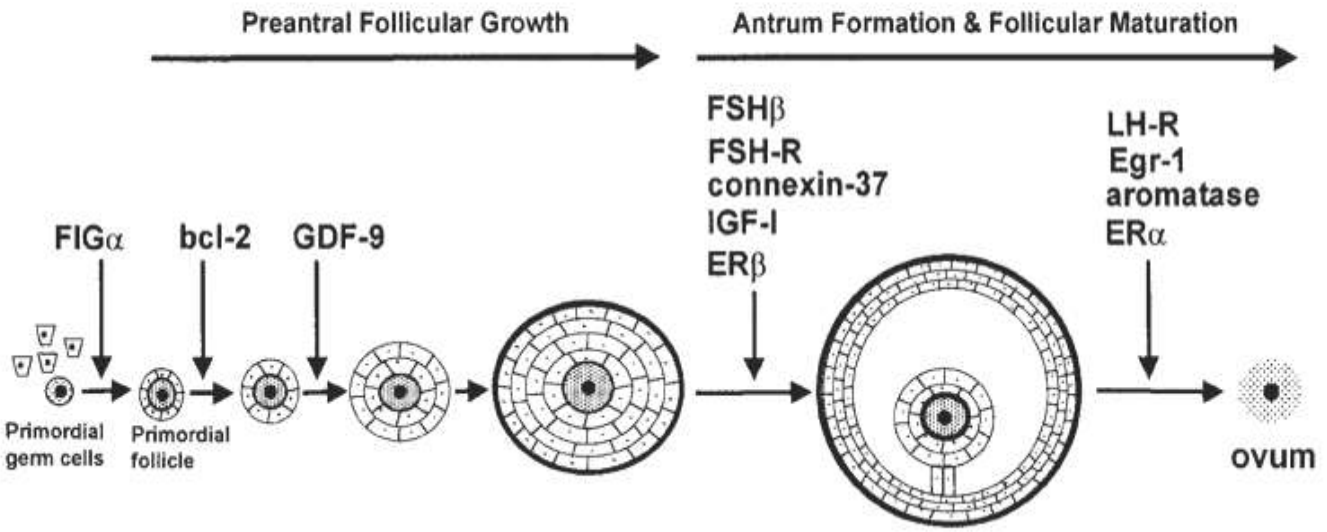
Steroidogenesis

Functional anatomy of the ovary



Carr and Wilson, 1987

Gonadotropin-independant → Gonadotropin-dependent



Primordial follicles:
ovum + unicellular layer of granulosa cells

Primary follicles:
ovum growing + additional layers of granulosa cells

Primary follicles:
ovum growing + granulosa + theca cells (originating from ovarian stroma)

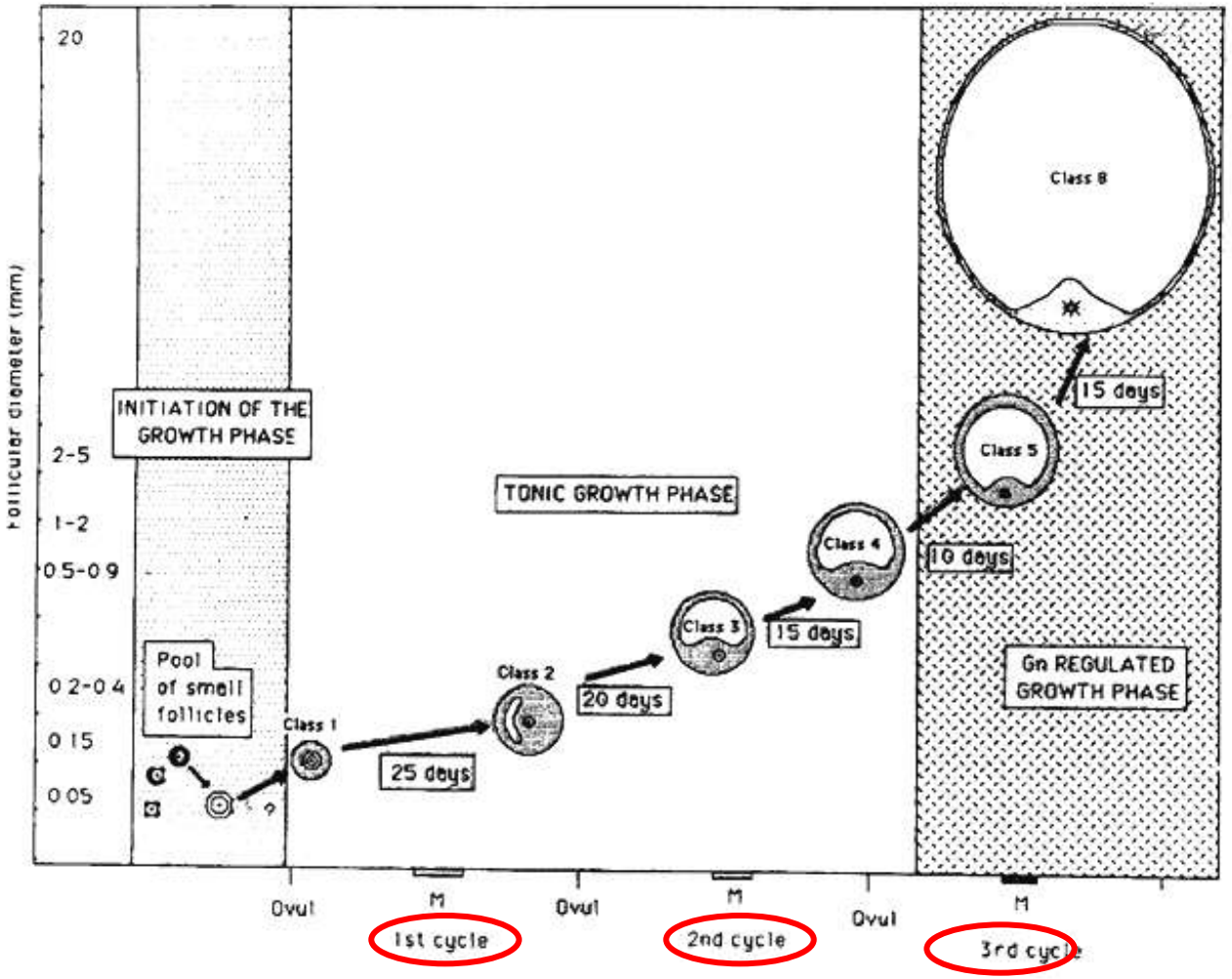
Accelerated growth of theca and granulosa cells, stimulated by gonadotrophins

Secretion of follicular fluid (rich in E2) by theca and granulosa cells : apparition of antrum

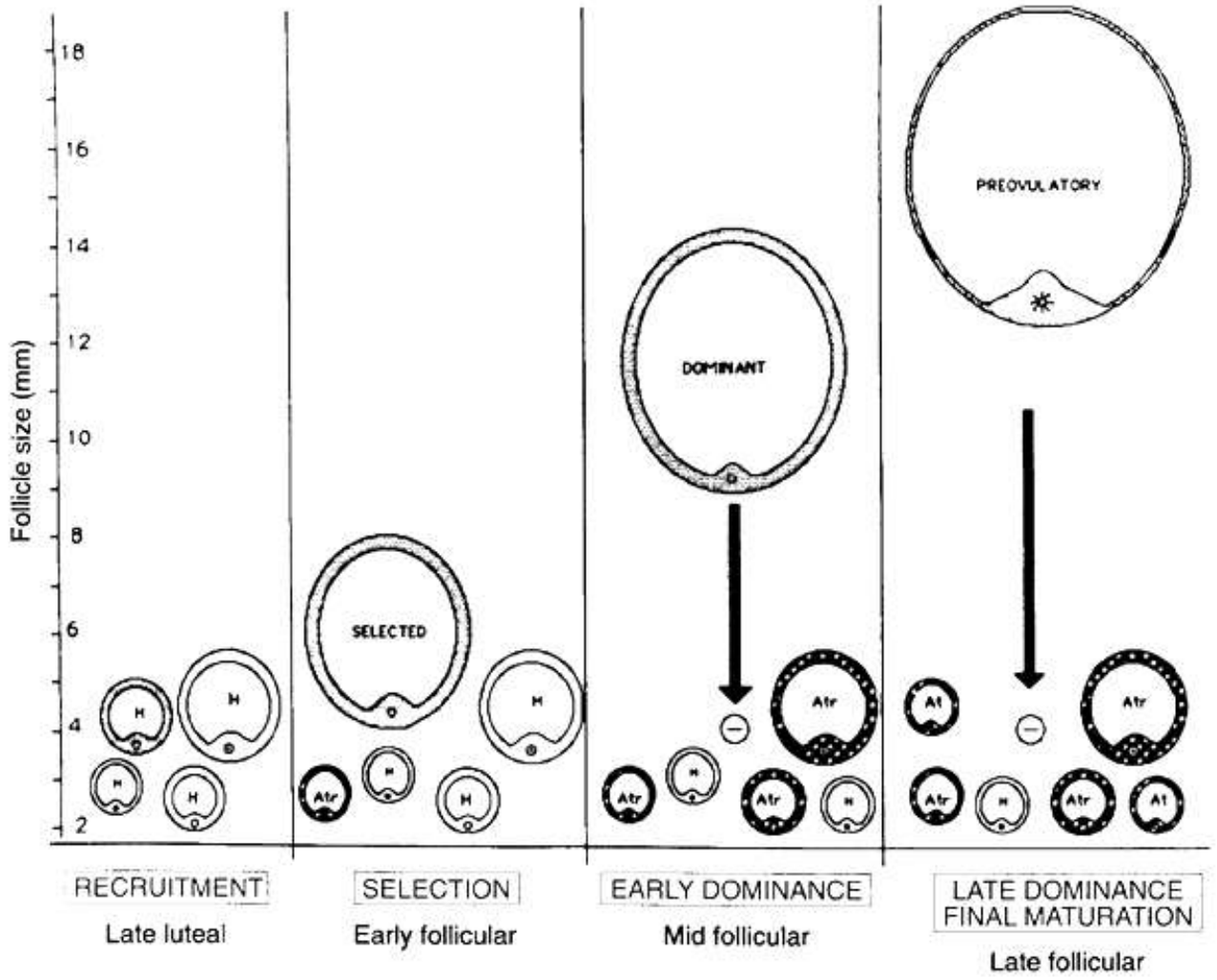
Simpson *et al,* Am J Med Genet 1999

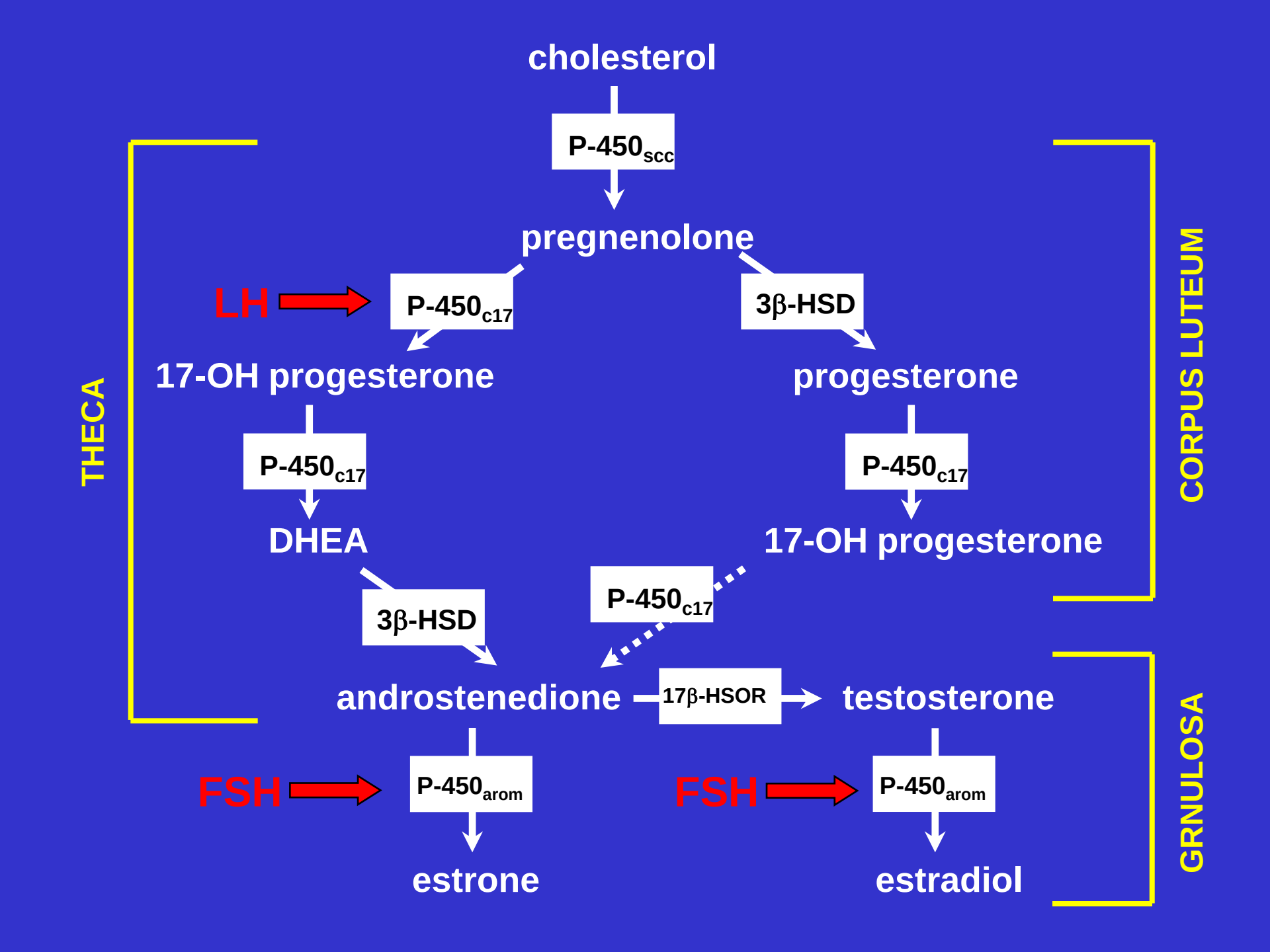
Gonadotropin-dependent

Highly gonadotropin-dependent

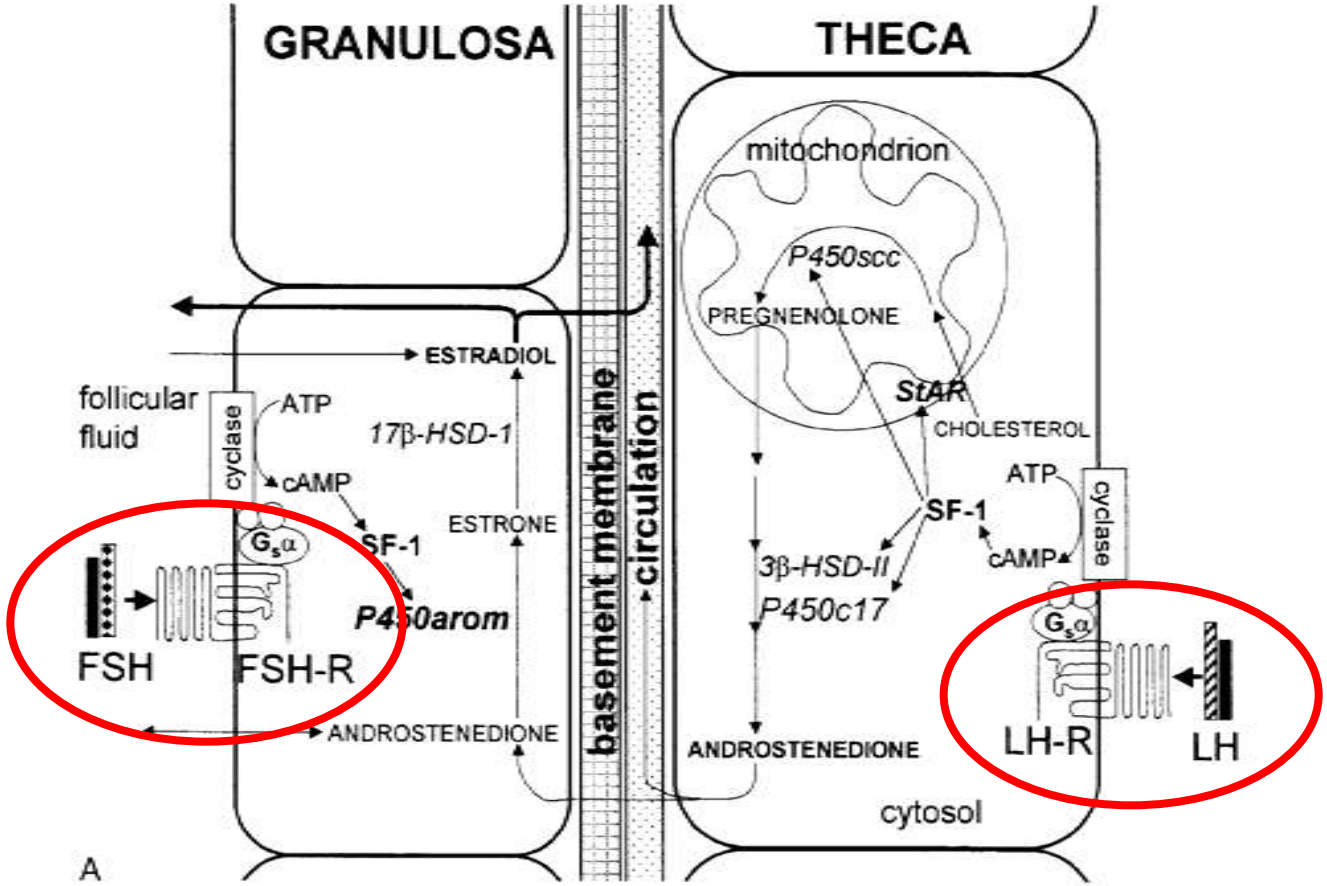


Follicular growth, gonadotropin dependent

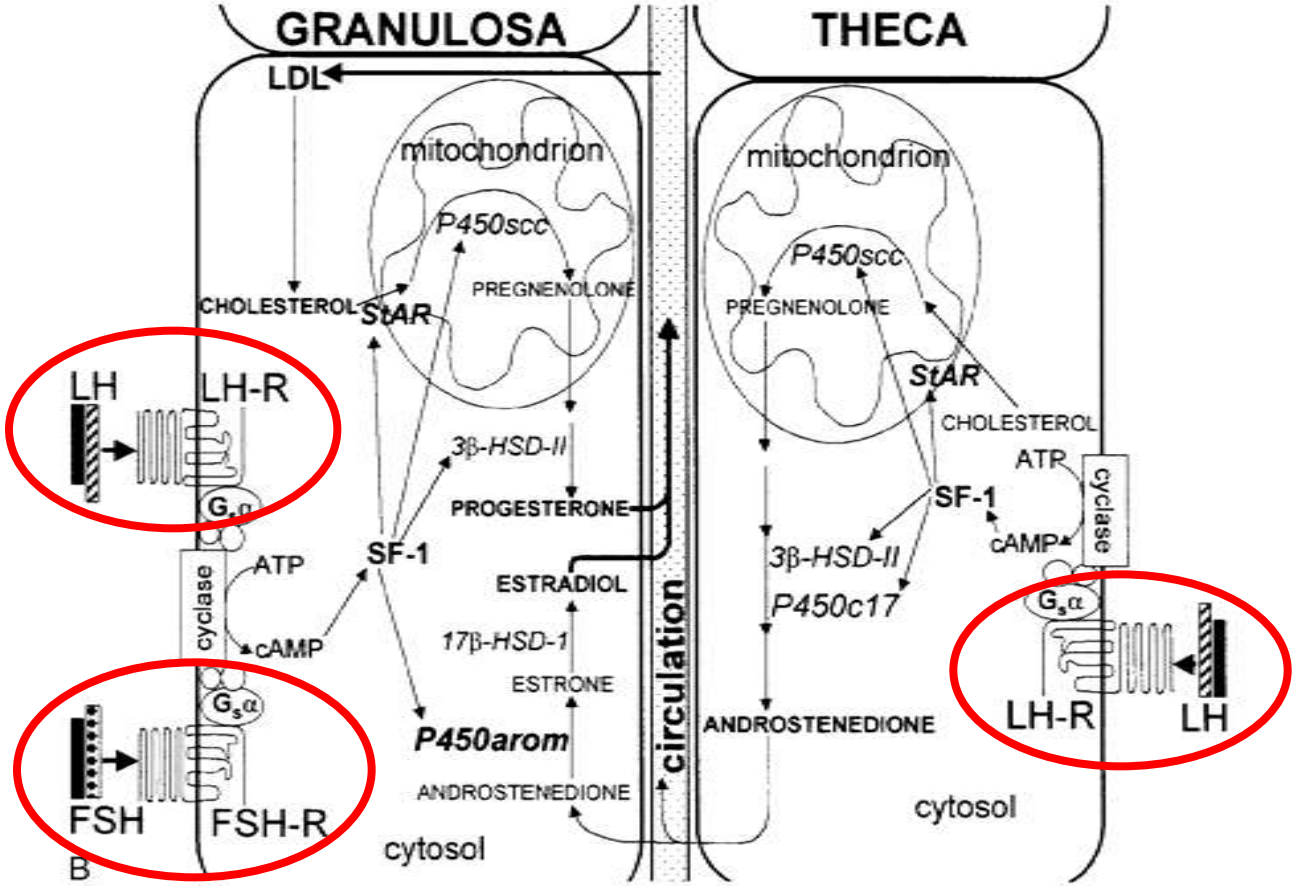



cholesterol
P-450scc
pregnenolone
LH
P-450c17
3β-HSD
17-OH progesterone
progesterone
P-450c17
P-450c17
DHEA
17-OH progesterone
P-450c17
3β-HSD
androstenedione
17β-HSOR
testosterone
FSH
P-450arom
FSH
P-450arom
estrone
estradiol
THECA
CORPUS LUTEUM
GRNULOSA

The two cell hypothesis in a pre-ovulatory follicle



The two cell hypothesis in the corpus luteum



Effects of oestrogens

On uterus : growth at puberty; increase in size of fallopian tubes

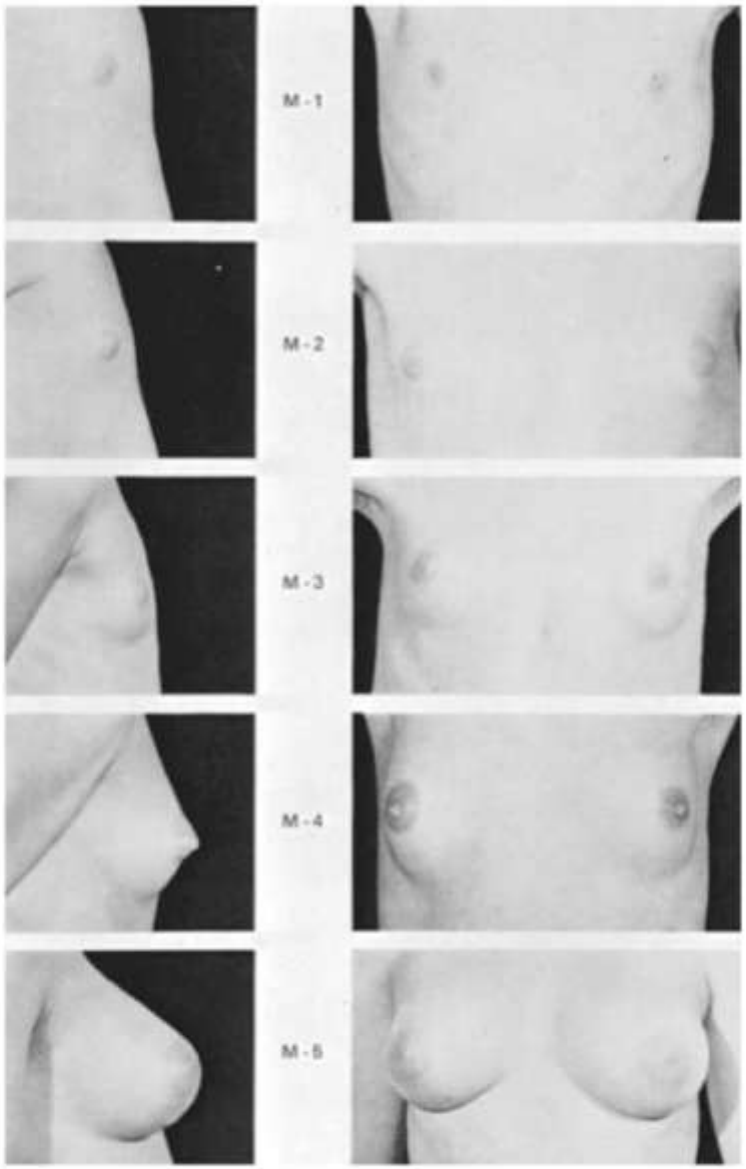
On vagina: increase in size; transformation of epithelium, from cuboid to stratified.

On endometrium: prolifération of endometrium; apparition of endometrial glands, useful to implantation and nutrition of fecondated ovum.

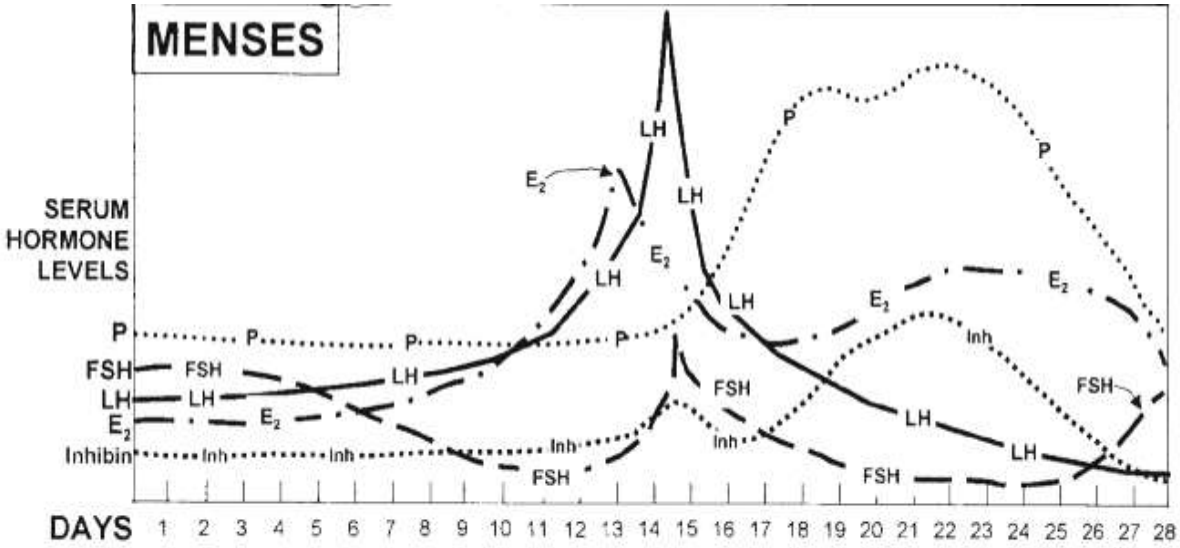
Effects of oestrogens

On bone : increase of osteoblastic activity; closure of epiphyses.

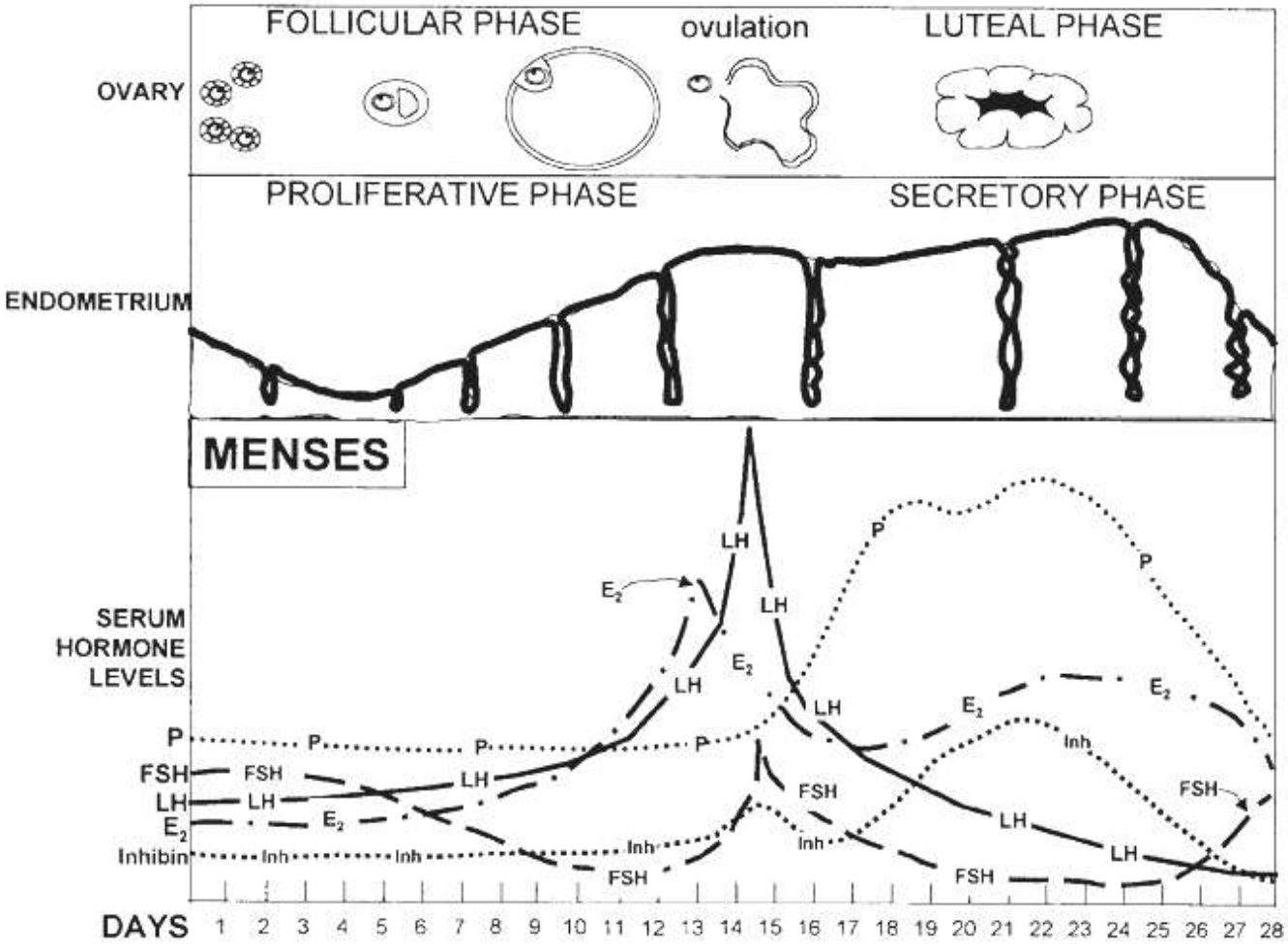
On adipose tissue: female-like repartition of fat (mammary gland, thighs)



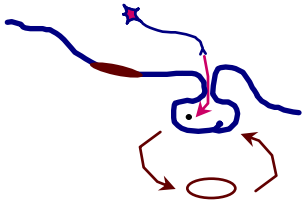
The menstrual cycle



The menstrual cycle



FSH Deficiency - Females



FSHβ

Three cases described

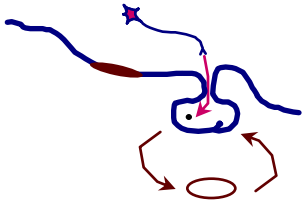
- **Phenotype:**
  - delayed puberty
  - primary amenorrhea
  - normal response to FSH with achivement of fertility

FSH-R

Finnish study

- **Phenotype:**
  - primary amenorrhea
  - ovarian dysgenesis with normal karyotype

FSH Deficiency - Males



FSHβ

Two cases described

- **Phenotype:**
  1) delayed puberty, low testosterone and absent spermatogenesis

  2) normal puberty and virilization, spermatogenic arrest

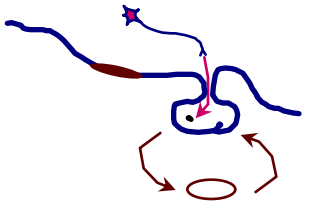
FSH-R

Finnish study

- normal virilization
- decreased testicular volume
- variable suppression of spermatogenesis

Role of the FSH/FSH-R System

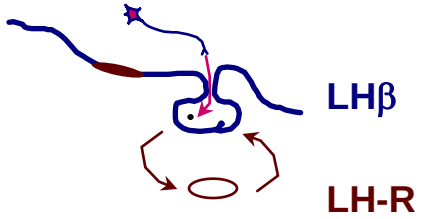
- **Important for estrogen production, follicular maturation and fertility**
- **Role of FSH in spermatogenesis remains unclear:**
  - **variable spermatogenesis in FSH-R mutations**
  - **absent spermatogenesis in FSHβ mutations**



FSHβ

FSH–R

LH Deficiency - Females

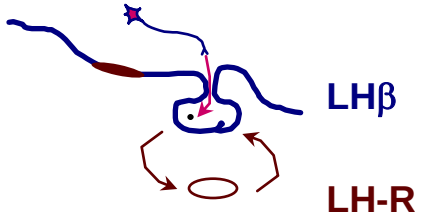


No LH-β mutation yet described in a female patient

LH-R

- normal external genitalia
- normal pubertal development
- primary amenorrhea
- **no pre-ovulatory follicles**

LH Deficiency - Males



LHβ

Two cases described

Bio-inactive LH

Impaired heterodimer

- **Phenotype:**
  - normal male
  - delayed puberty
  - response to hCG:

LH-R

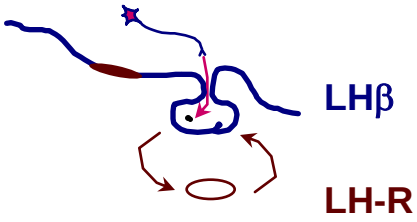
Broad spectrum of phenotypic expression of inactivating mutations

- pseudohermaphroditism and complete azoospermia
- micropenis, delayed puberty and arrest of spermatogenesis

Role of the LH/LH-R System

- **Important for normal male development**
- **LH-R plays a role in spermatogenesis as well as ovulation**

LH-R is a candidate gene for male as well as female infertility



Amenorrhea

Primary or secondary

Differential diagnosis

- **Physiological processes :**
  Pregnancy, menopause
- **Congenital or acquired anomalies**
- **Hypothalamic pathologies:** ***hypogonadotrope amenorrhea (low LH and FSH)***
- **Ovarian pathologies:** ***hypergonadotrope amenorrhea (high LH and FSH)***

Ovarian insufficiency

Genetic anomalies

- **(Turner syndrome, FSH inactivating mutations)**

Precocious menopause

- **Acceleration of follicular atresia in women of childbearing age**

Chronic anovulation

- **Often secondary to other endocrine dysfunctions, obesity, or of toxic origin (drugs...)**

Polycystic ovarian syndrome

- **Most frequent endocrine pathology**

Consequences of amenorrhea

- Menstrual dysfunction
- Hirsutism/acne (androgene excess)
- Infertility
- Increased risk of endometrial cancer
- Possible increased risk of breast cancer
- Increased cardio-vascular risk
- Increased incidence of diabetes mellitus
- Increased risk of osteoporosis

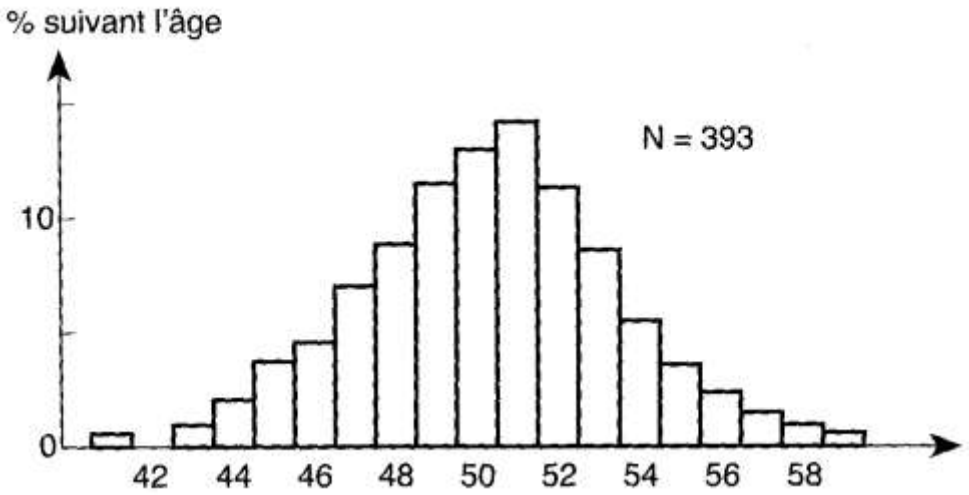
Consequences of amenorrhea

All occurences of amenorrhea must be worked up, and then taken care of.

Age at menopause in Switzerland

Mean 50 yrs

- precocious <40 yrs
- late >55 yrs



Factors influencing the age at menopause:

Heredity, smoking, ethnical background, climate (?)

Female life expectancy (1997): 82.3 yrs

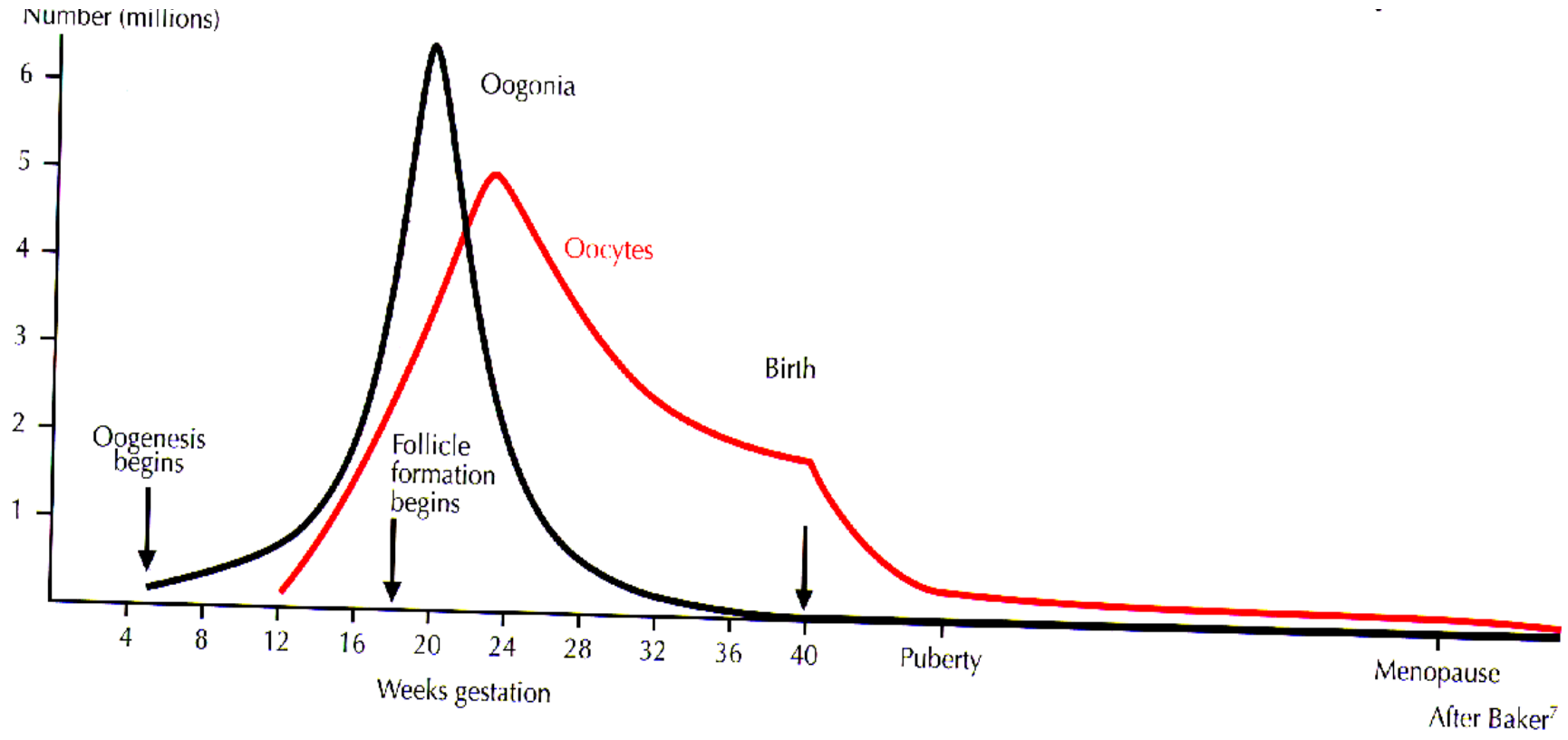
32.3 yrs in menopause

Physiopathology of menopause: the apoptose phenomenon

Landmarks in ovocyte count in the human

- Fœtus: 7 millions
- Birth: 1-2 millions
- Puberty: 400 000

Follicular depletion accelerates at around 37 yrs: imbalance beetween pro-apoptotic (Bax) and anti-apoptotic (Bcl2) transcription factors

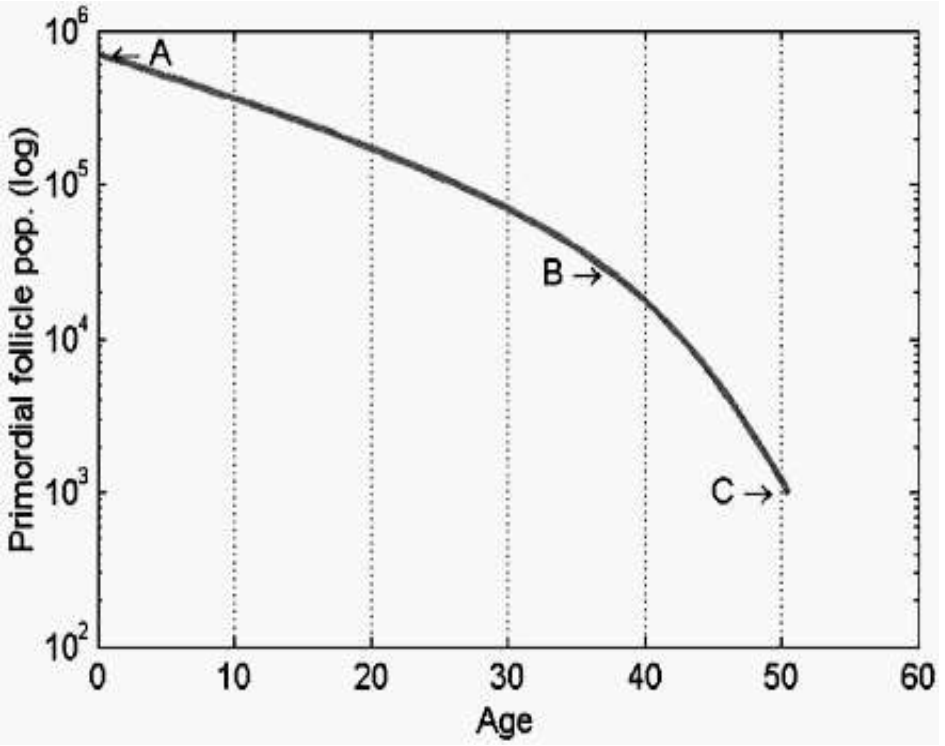

Number (millions)
6
5
4
3
2
1
Oogonia
Oocytes
Birth
Oogenesis begins
Follicle formation begins
4
8
12
16
20
24
28
32
36
40
Puberty
Menopause
Weeks gestation
After Baker[7]

Evaluation of ovocyte depletion
The Faddy-Gosden equation

$$Dy/dx=-y[0.0595+3716(11780+y)]$$

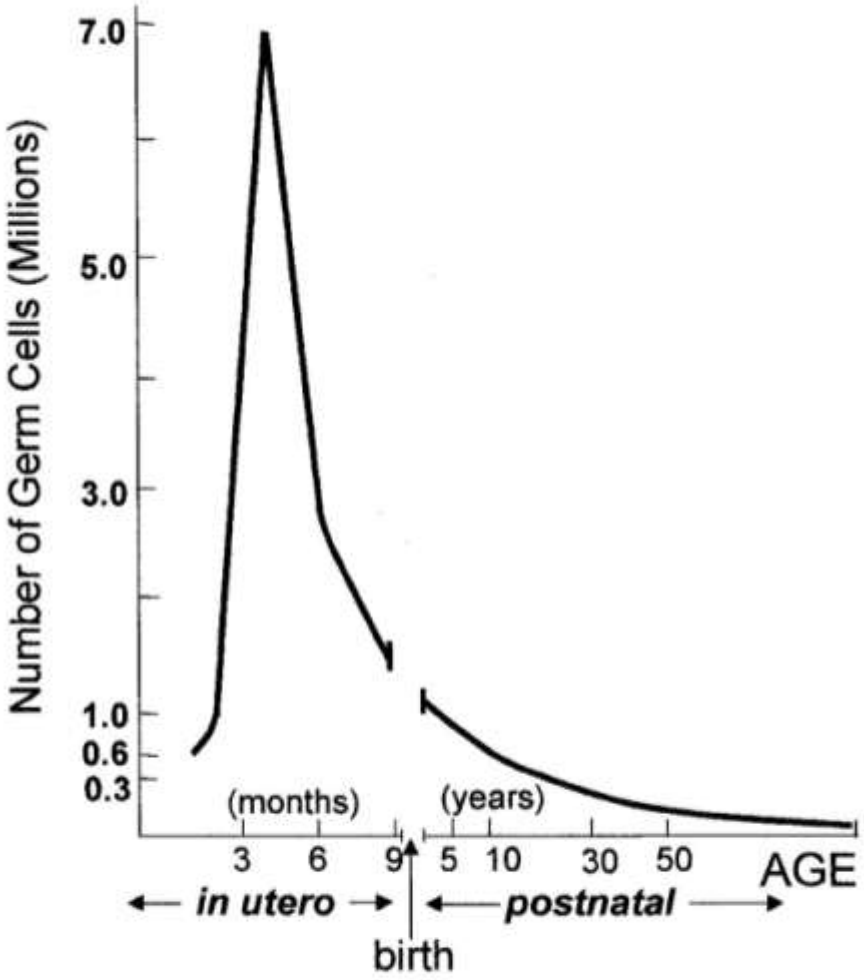
X=age
Y=number of primordial follicles

A=701 000 follicles
B=25 000 follicles
C=1000 follicles



Faddy et al. Hum Reprod 1996,7, 1342-1346

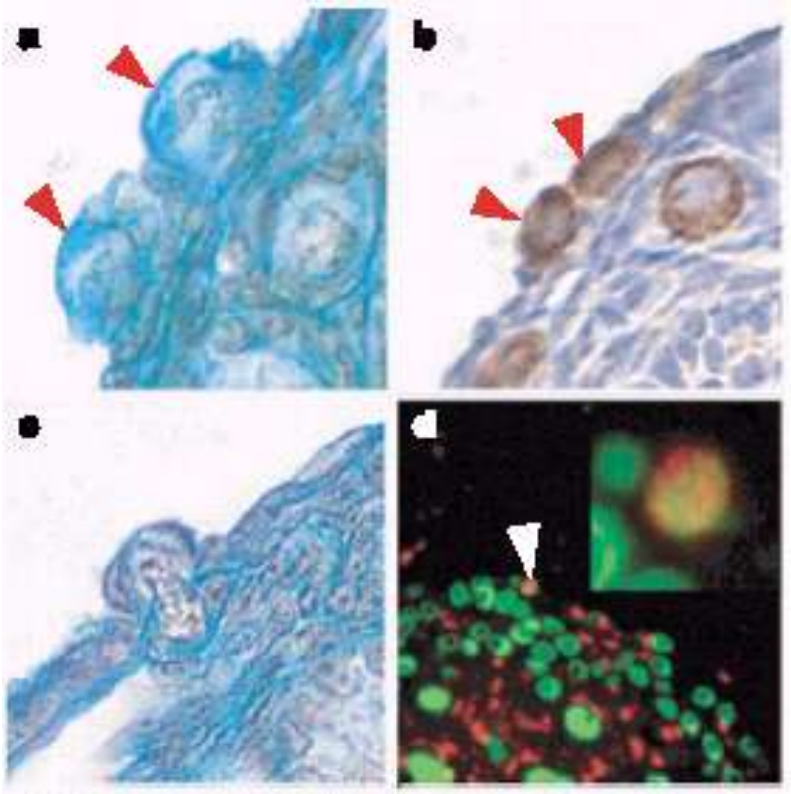
Production of germinal stem cells by the ovary



Germline stem cells and follicular renewal in the postnatal mammalian ovary

Joshua Johnson*, Jacqueline Canning*, Tomoko Kaneko, James K. Pru & Jonathan L. Tilly

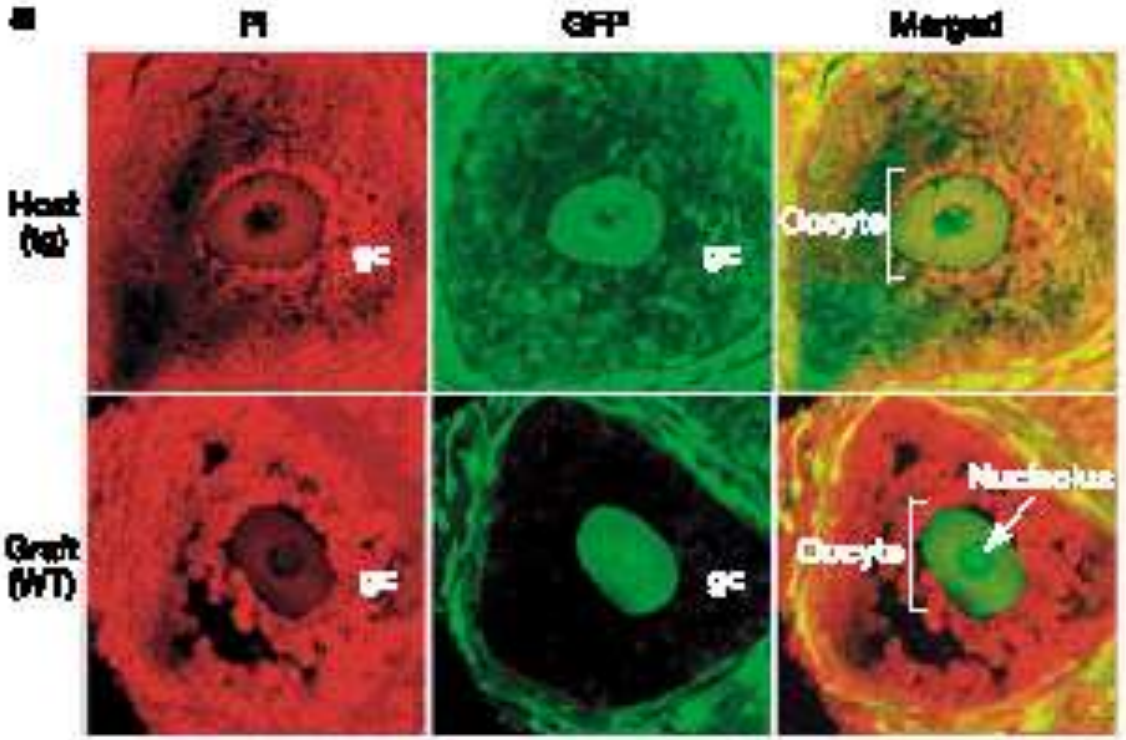
- Germline stem cells present in the ovary, outside follicles
- These stem cells are dividing



Nature, Mars 2004

Germline stem cells and follicular renewal in the postnatal mammalian ovary

•Germline stem cells transplanted into recipient ovaries produce new follicles



Nature, Mars 2004