

La Sterilità



dr m.m. schönauer

Ob-Gyn Ferrara

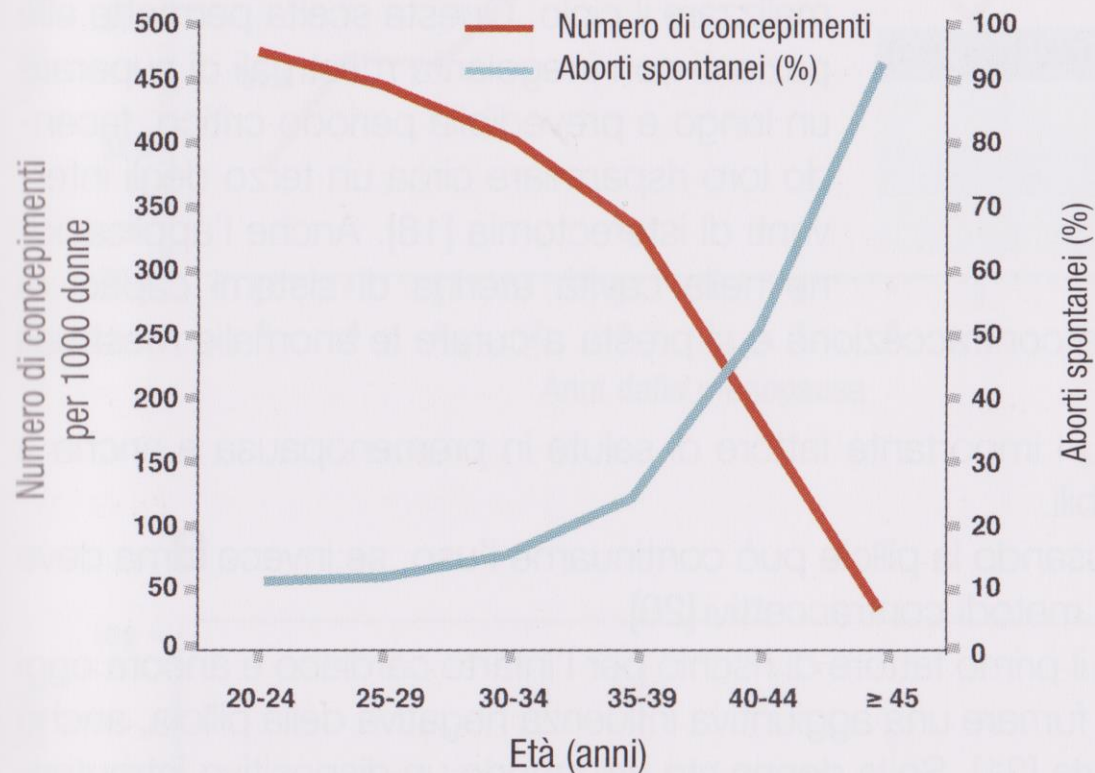
Dir. Prof. P.F. Greco



Madame d'Estrée and one of her Sisters (1571)

di gravidanze si riduce, ma cresce anche il numero di gravidanze a rare feti malformati o ad abortire (FIGURA 4).

FIGURA 4 Diminuzione delle nascite e aumento degli aborti spontanei in funzione dell'età materna [15].



così frequenti gli errori genetici? I due gameti, ovocita e spermatozoi, si uniscono per trasferire i caratteri ereditari al neonato. Affinché le cellule dell'e

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COH (*controlled ovarian hyperstimulation*)

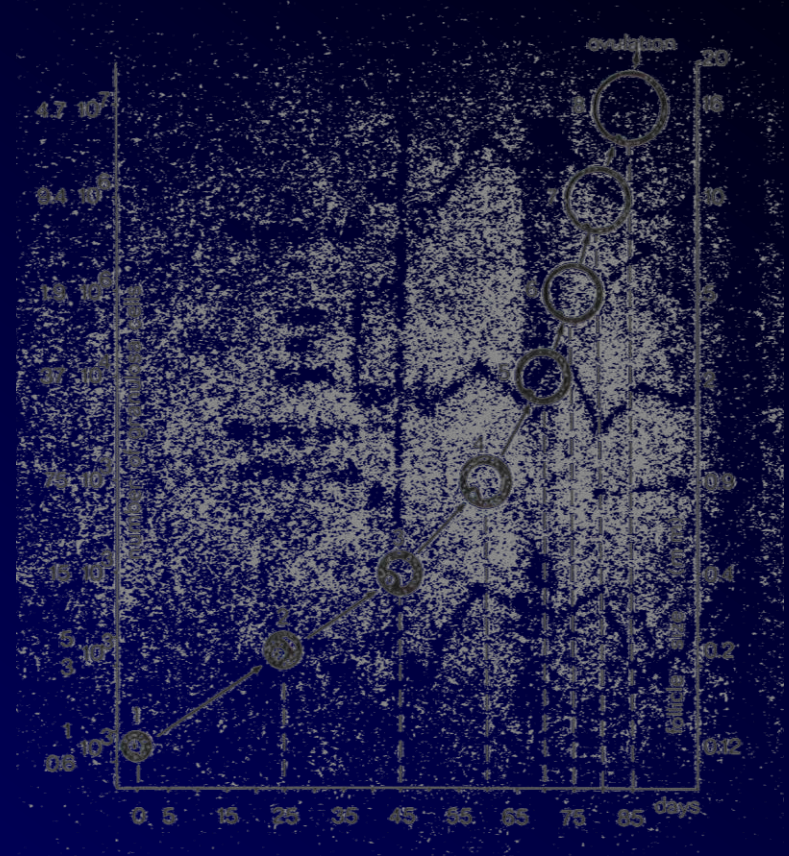
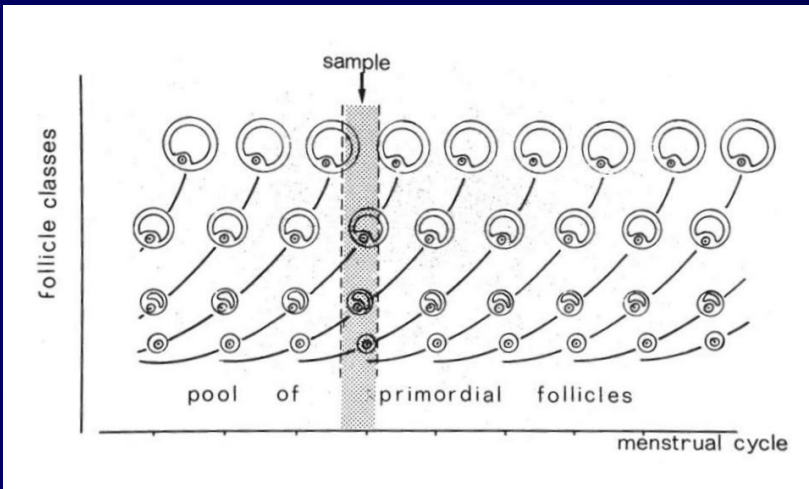
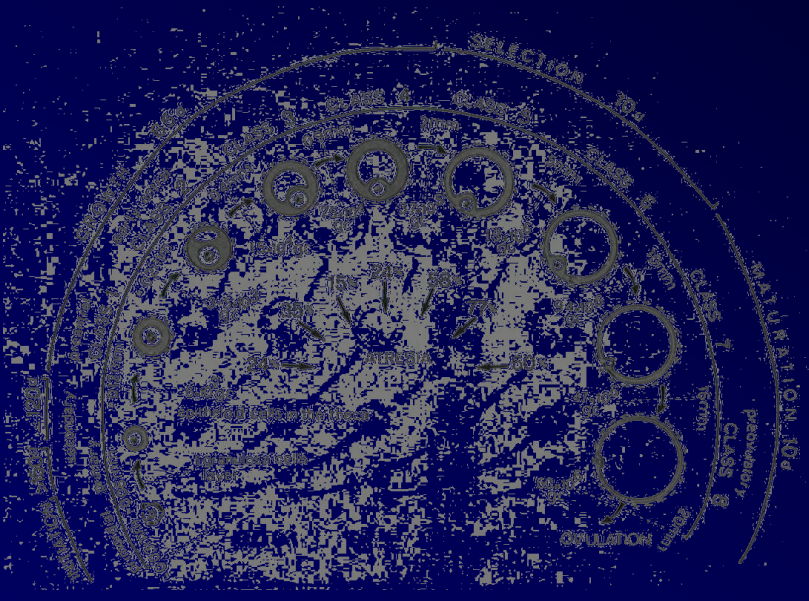
Objective:

➡ Induction of multiple follicular maturation

- Adequate follicular quality
- Adequate follicular number
- **Synchronization** (concomitant development)

➡ Improvement of embryo selection for transfer

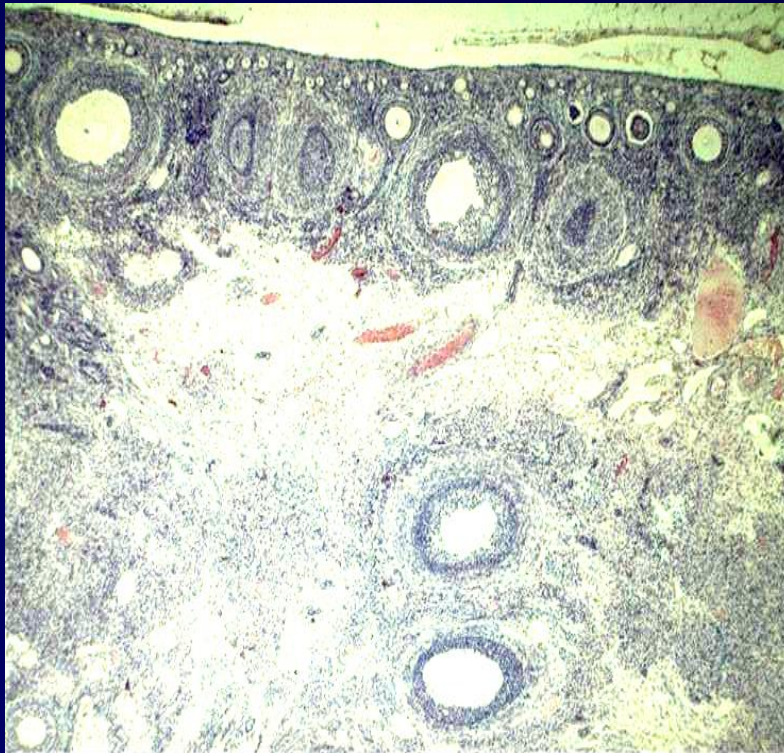
Physiology



Follicular reserve
Follicular cohort (pool)

Folliculogenesis

Ovary: heterogeneous follicular reserve



➔ Resting phase

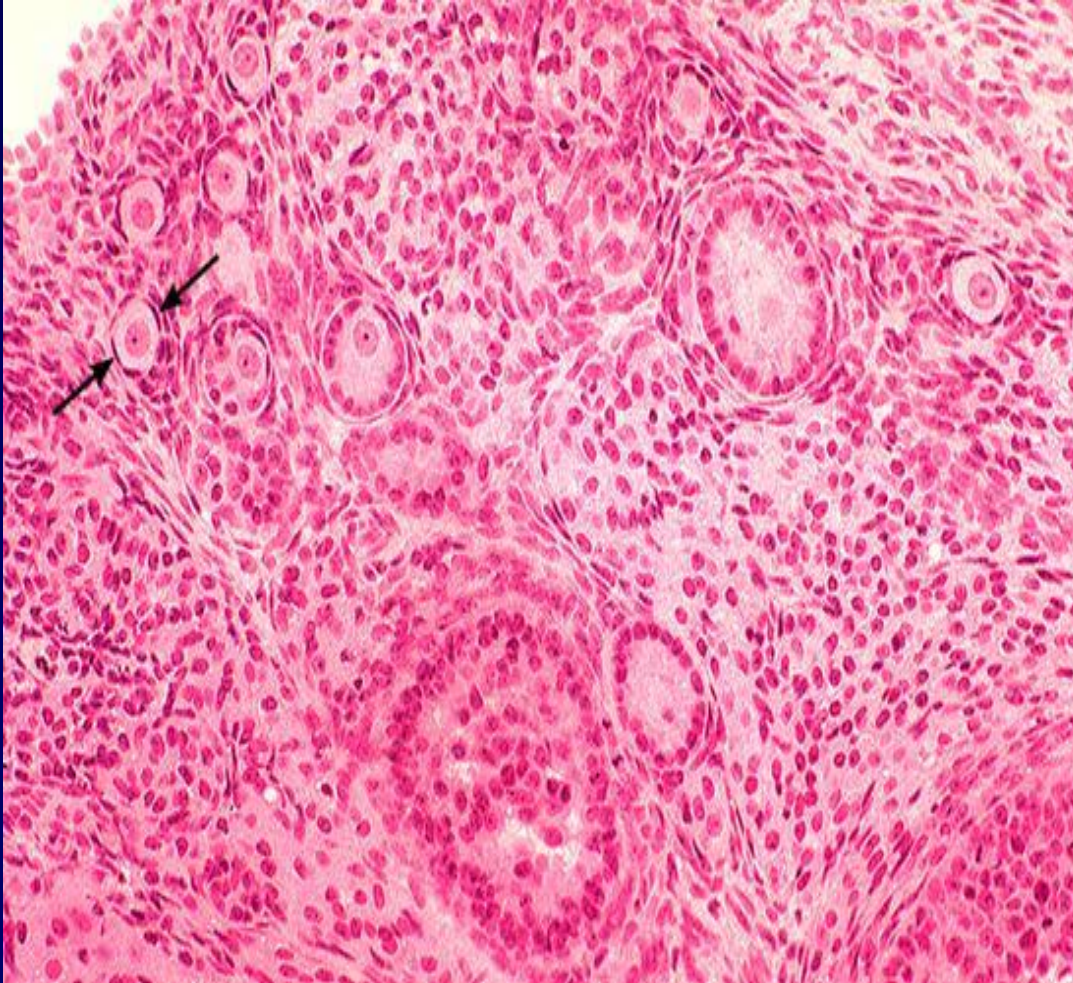
➔ Basal growth phase

➔ Selection phase

➔ Maturation phase

Primordial follicle

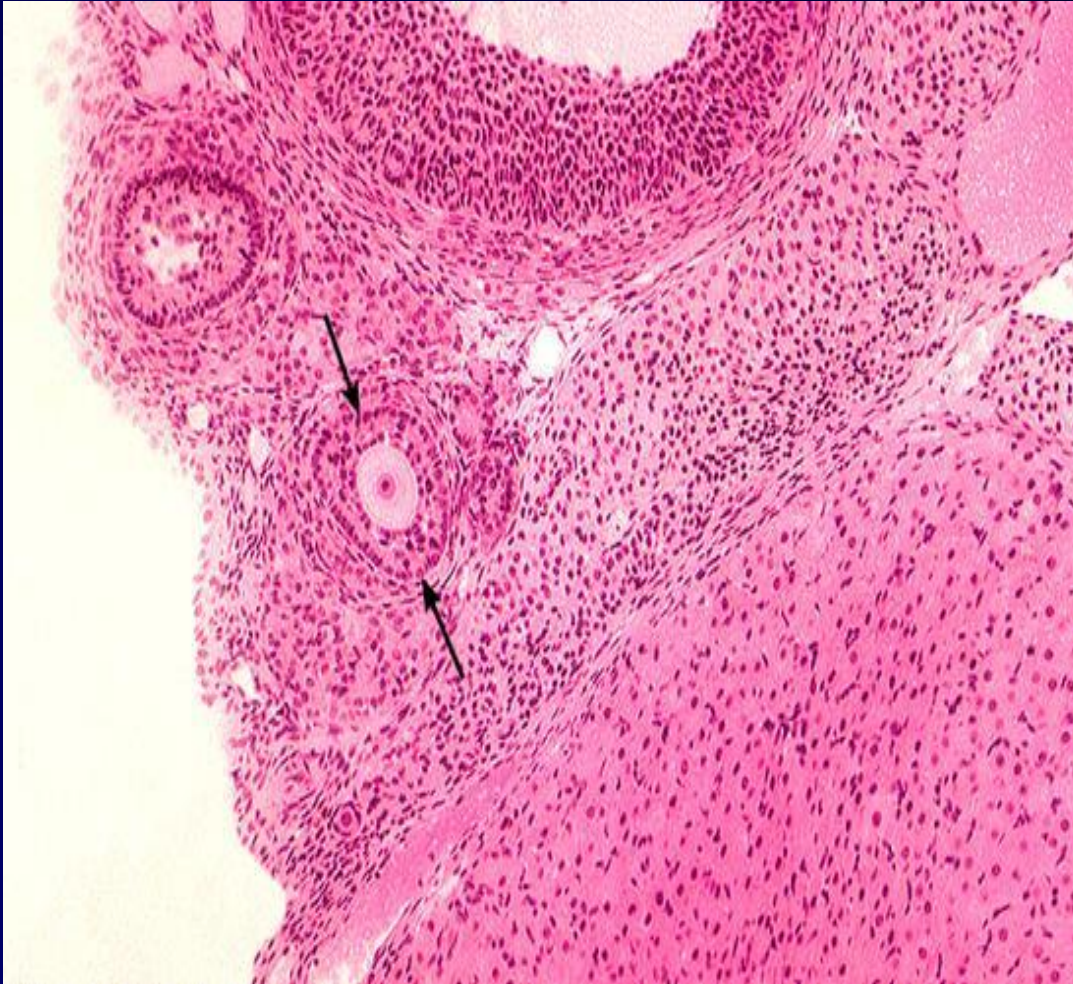
Resting phase



- 30-60 μm diam
- 1 layer
- CG spindle

Primary follicle

Resting phase



- 60-120 μm
- 1 layer
- CG cuboidal

Resting phase

Almost gonadotrophin independent:

- Growth factors (IGF-1, etc)

Zhou et al, Endocrinology, 1991

- Proto-oncogens

Motro et al, Dev Dyn, 1993

- Intra-ovarian inhibiting factors

Gougeon et al, End Rev, 1996

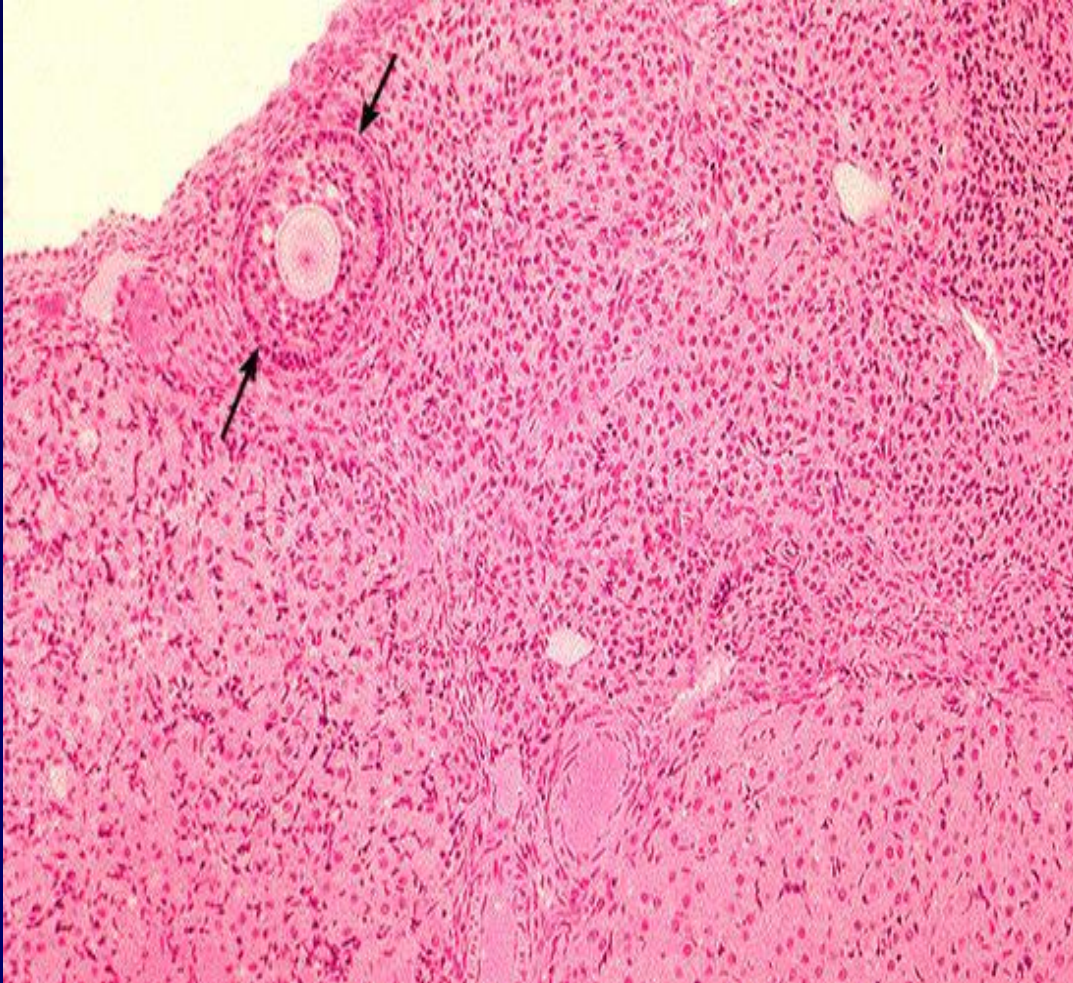
- GDF-9

Dong et al, Nature, 1996

Hsueh et al, Moll Cell Endocr, 2000

Basal growth phase

Secondary follicle



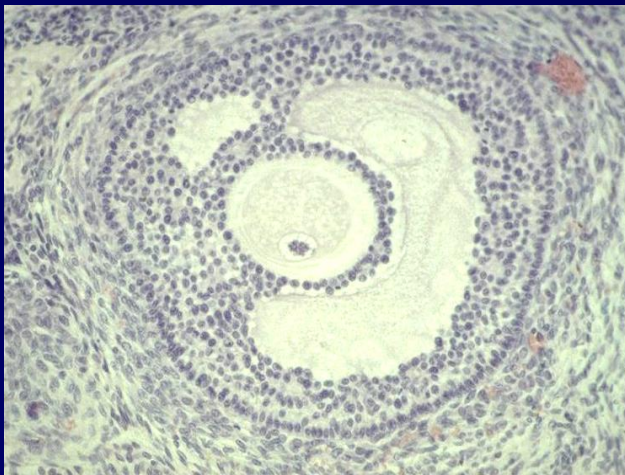
- 80-120 μm
- 3-6 layers
- CG cuboid
- theca
- vascularization

Basal growth phase

Pre-antral follicles

- Class 1 (<0.1mm)

Early antral follicles



- Class 2 (0.1- 0.4mm)

- Class 3 (0.5-0.9 mm)

- Class 4 (0.9-1.9 mm)

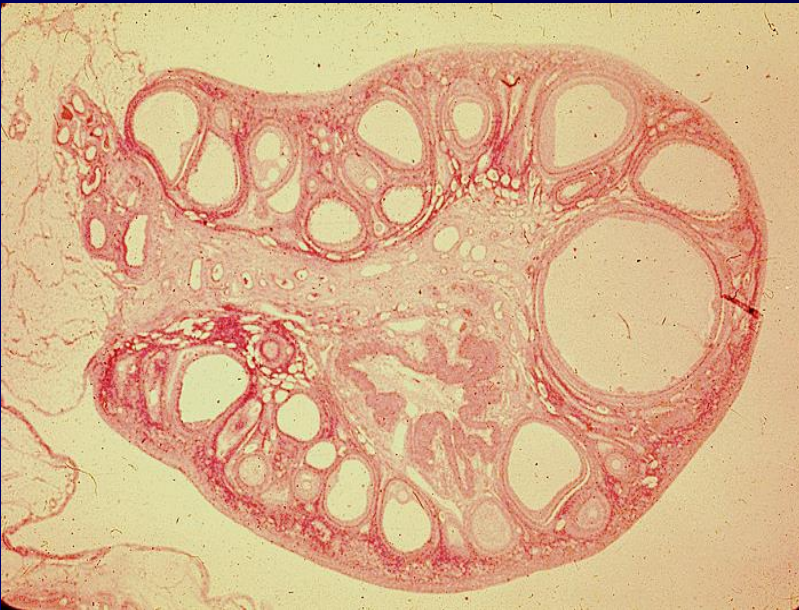
25 d

20 d

15 d

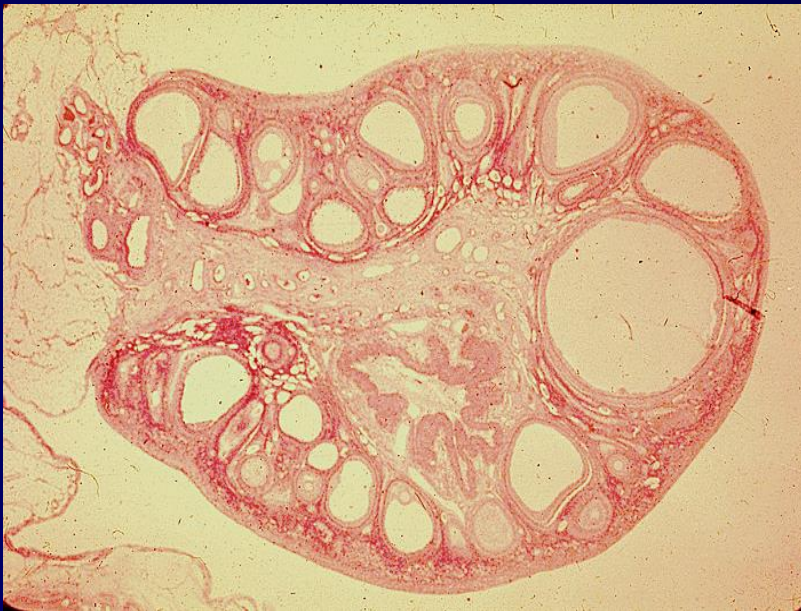
Selection phase

Selectable follicular cohort



Selection phase

Selectable follicular cohort



- Early follicular phase
- 2-8 mm diameter
- Class 5 (and 6)
- Gonadotrophin-dependent
- Hormonal production

Selection phase

Selectable follicular cohort

- US assessment



Selection phase

Selectable follicular cohort



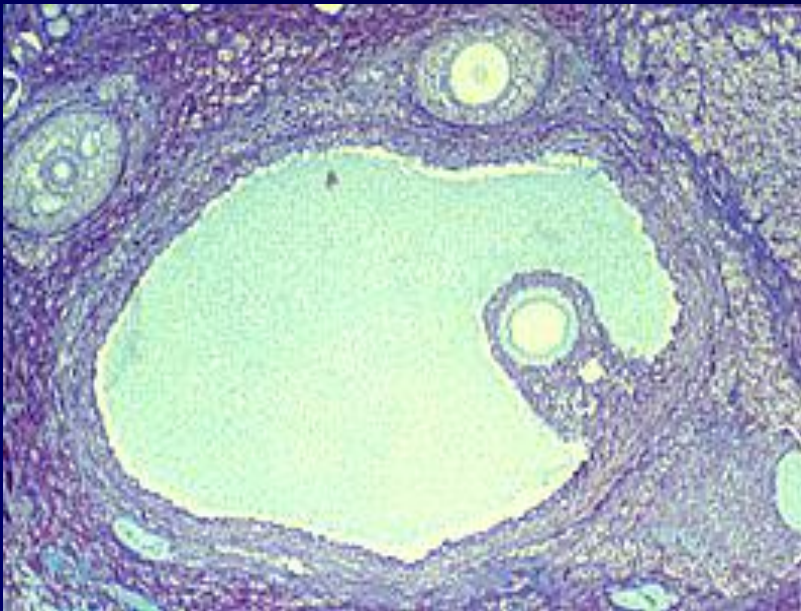
Higher FSH sensitivity

Gougeon et al, Fertil Steril, 1990

E_2 and inhibin B production

Selection phase

Selectable follicular cohort



Ovarian reserve
tests
physiological base

Physiology

Ovarian ageing

- Lower inhibin B production (smaller follicular cohort)
- Higher FSH
- Premature LH peak higher risk
- Early luteinization (more LH receptor)
- Increased P/E2 in late follicular phase in COH

(Luborsky JL, 2002)

(Younis JS, 2001)

Poor responders

- Elderly patients with an abnormal endocrinological profile
- Young patients with an altered endocrinological profile
- Young patients with a normal basal profile
- Specific pathologies (e.g. Steinert)

(Barri P, 2000)

Physiology

Ovarian ageing steps

- 1: normal cycles, small inhibin B reduction and little FSH increase
- 2: irregular cycles, higher FSH increase
- 3: irregular cycles, inhibin B reduction and E2 increase
- 4: no cycles, High FSH, very low E2 and inhibin B

(Burger HG, 1994)

Physiology

Woman has a limited follicular potential:

➡ During intra-uterine life:

- lost > 80% of follicular reserve
- Follicular atresia +++

Himelstein-Braw et al, J Reprod Fertil, 1976

➡ Puberty:

- About 300.000 follicles
- 400 - 500 ovulations

➡ Menopause:

- 100 - 1000 follicles

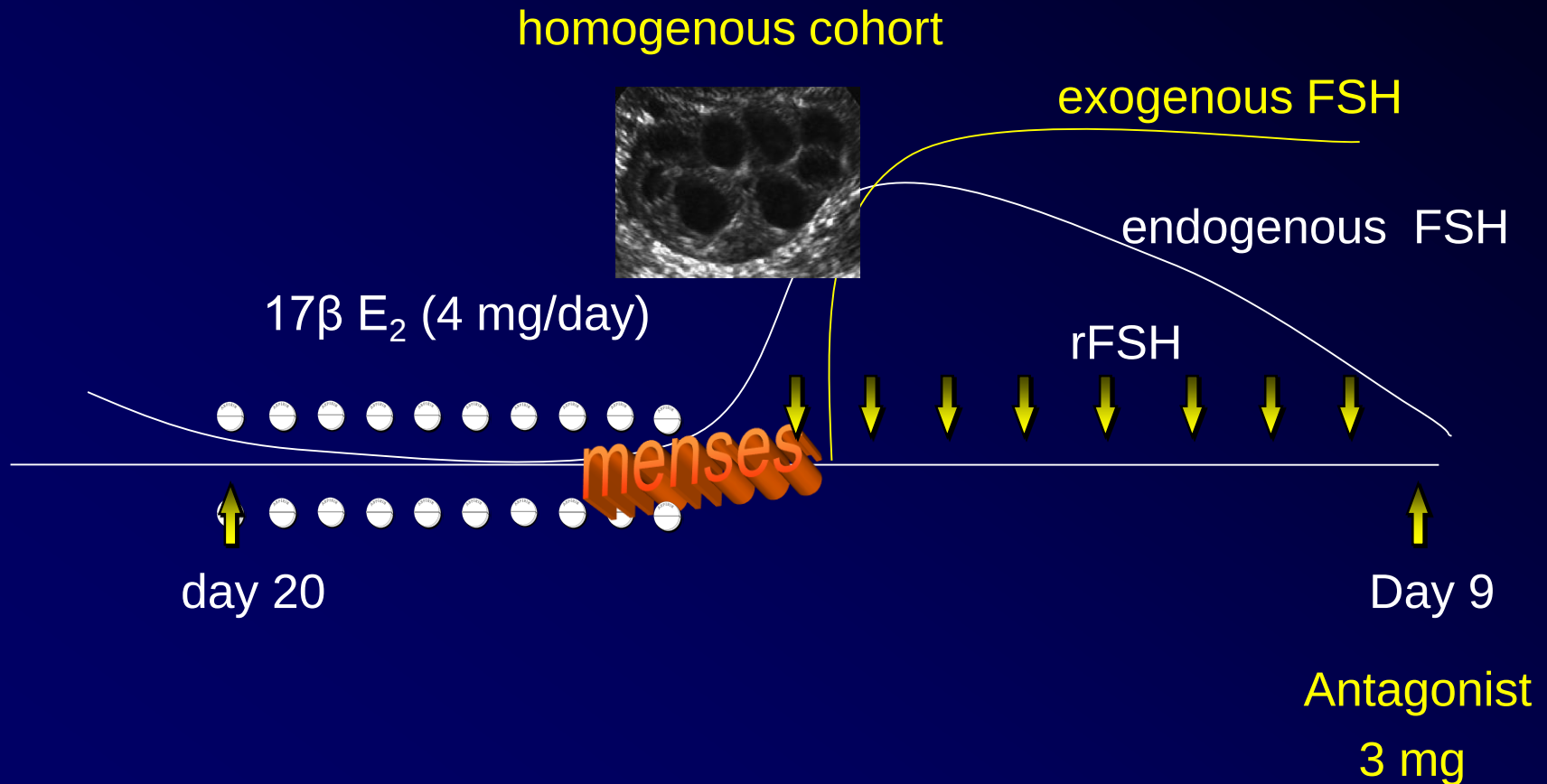
Gougeon et al, Biol Reprod, 1992

Faddy et al Acta Endocrinol (Copenh), 1992

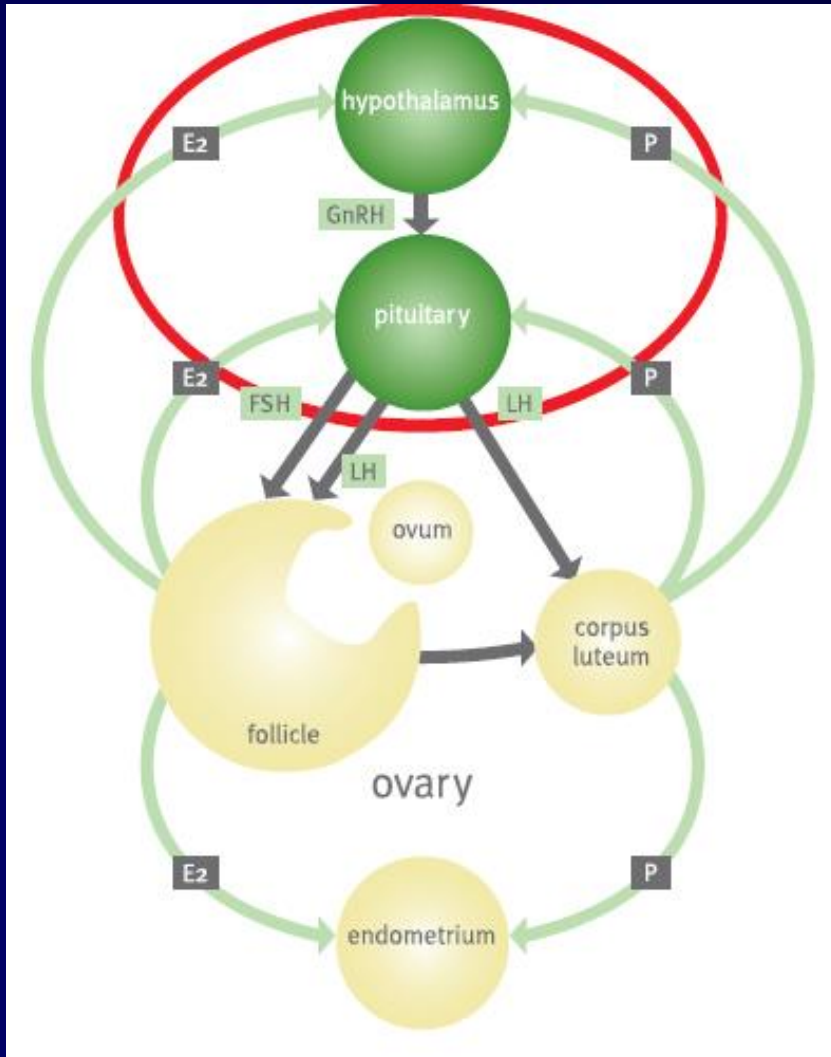
Pregnancy rate e Live birth rate in older patients in ART

Age	Patients	Completed cycles	Clinical Pregnancies(%)	Live births (%)
38	11	28	17.8	14.2
39	20	69	13	10.1
40	21	84	7	5.9
41	18	62	11	4.8
42	17	50	10	8.0
43	4	5	0	0
44	4	11	0	0
45	4	9	0	0
46	1	4	0	0
47	1	2	0	0

New strategies

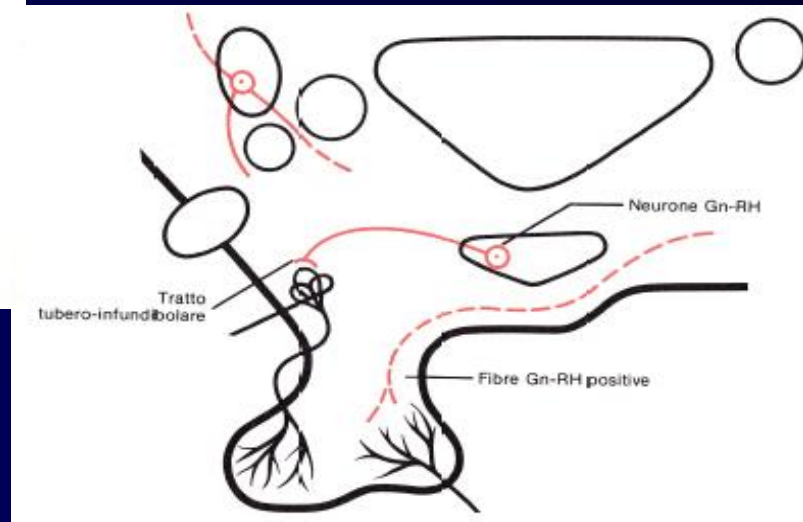
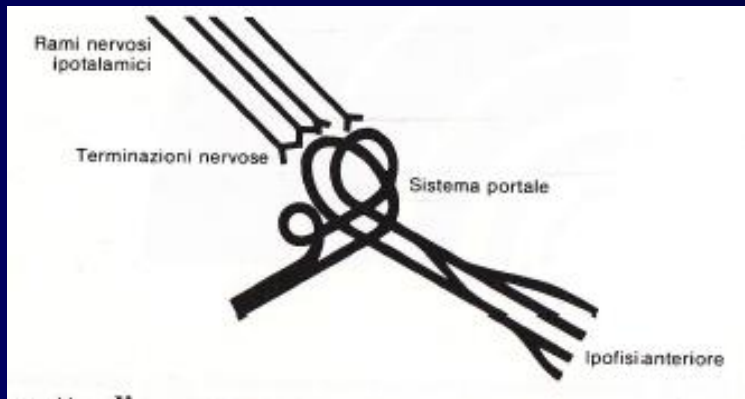


Sistema ipotalamo-ipofisi-gonadi



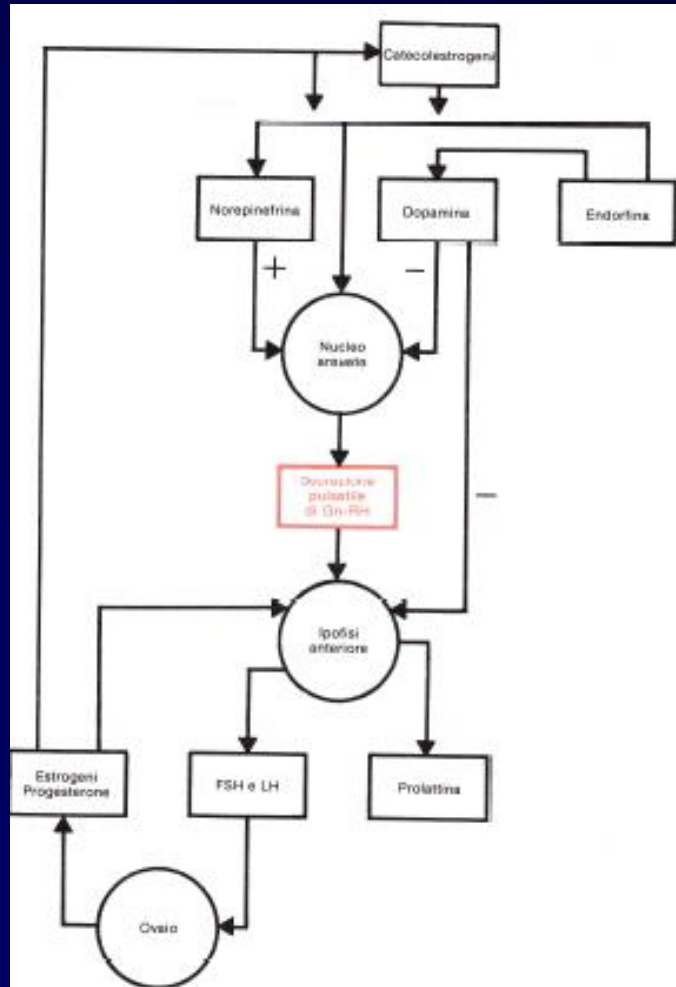
***Meccanismo azione
agonisti***

Meccanismo azione agonisti

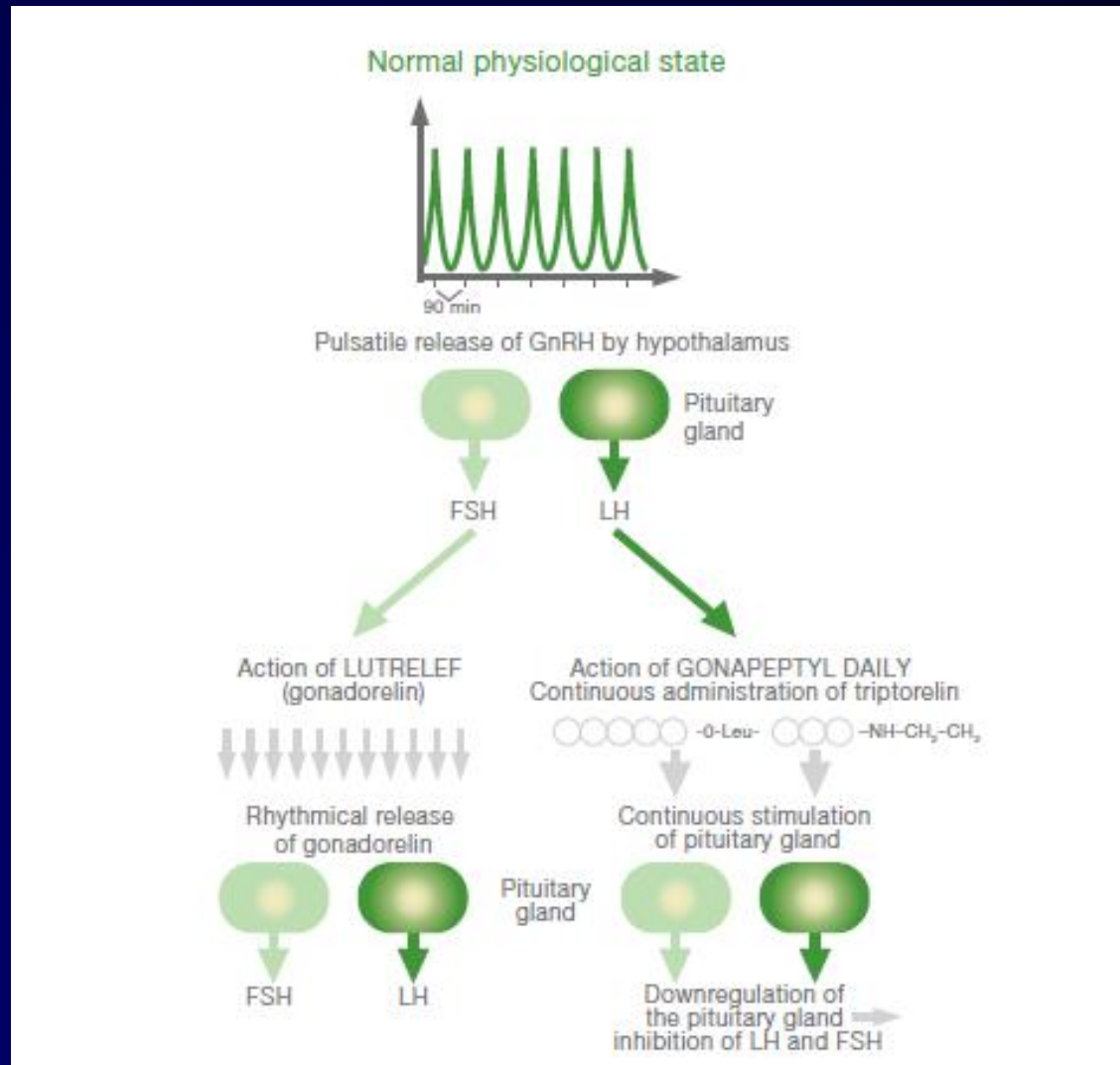


**Dosaggio max GnRH
nel sangue portale 2
ng/ml un impulso ora
di circa 6 min**

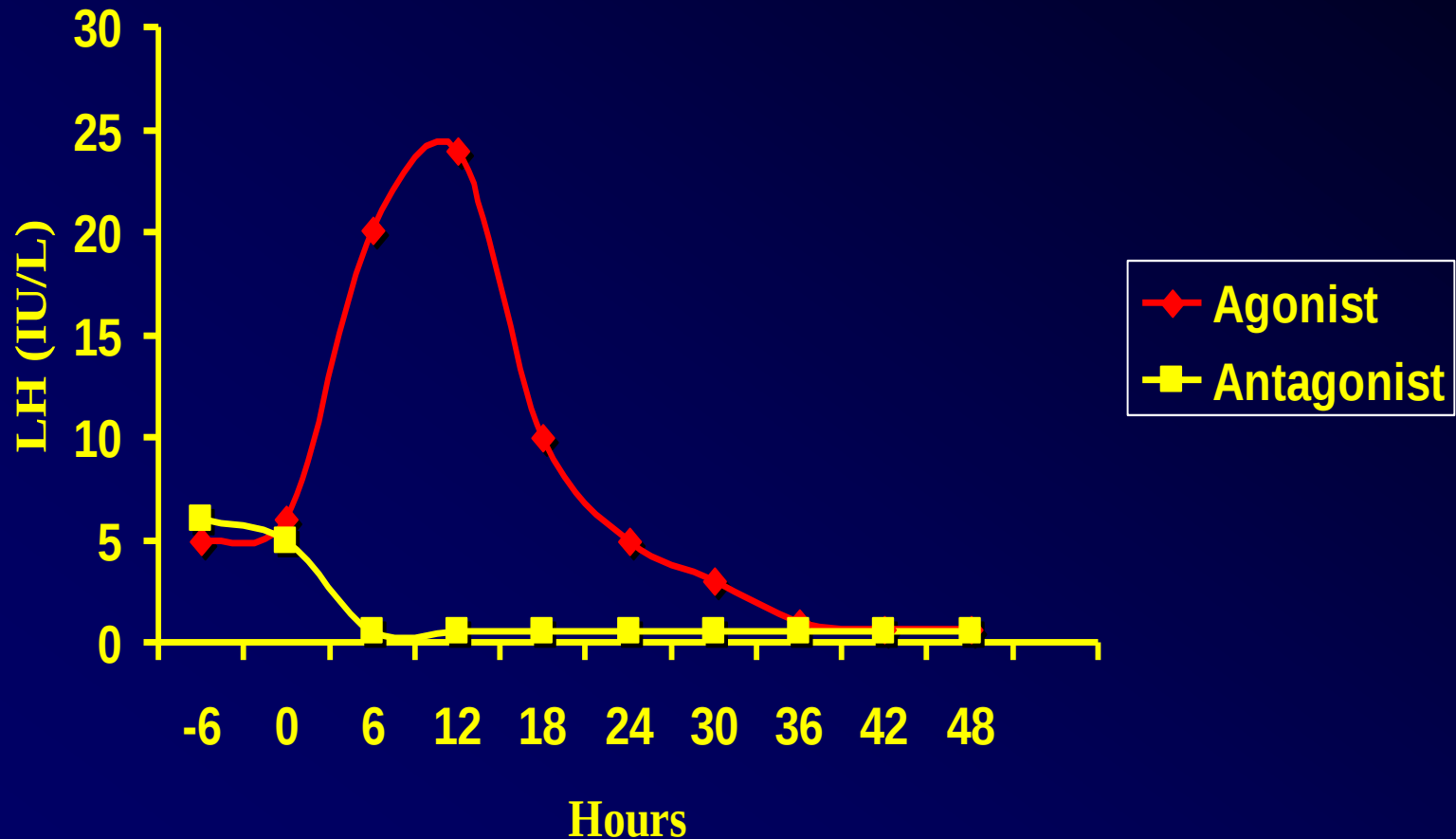
Meccanismo azione agonisti



Meccanismo azione agonisti GnRH



GnRH Agonist vs Antagonists

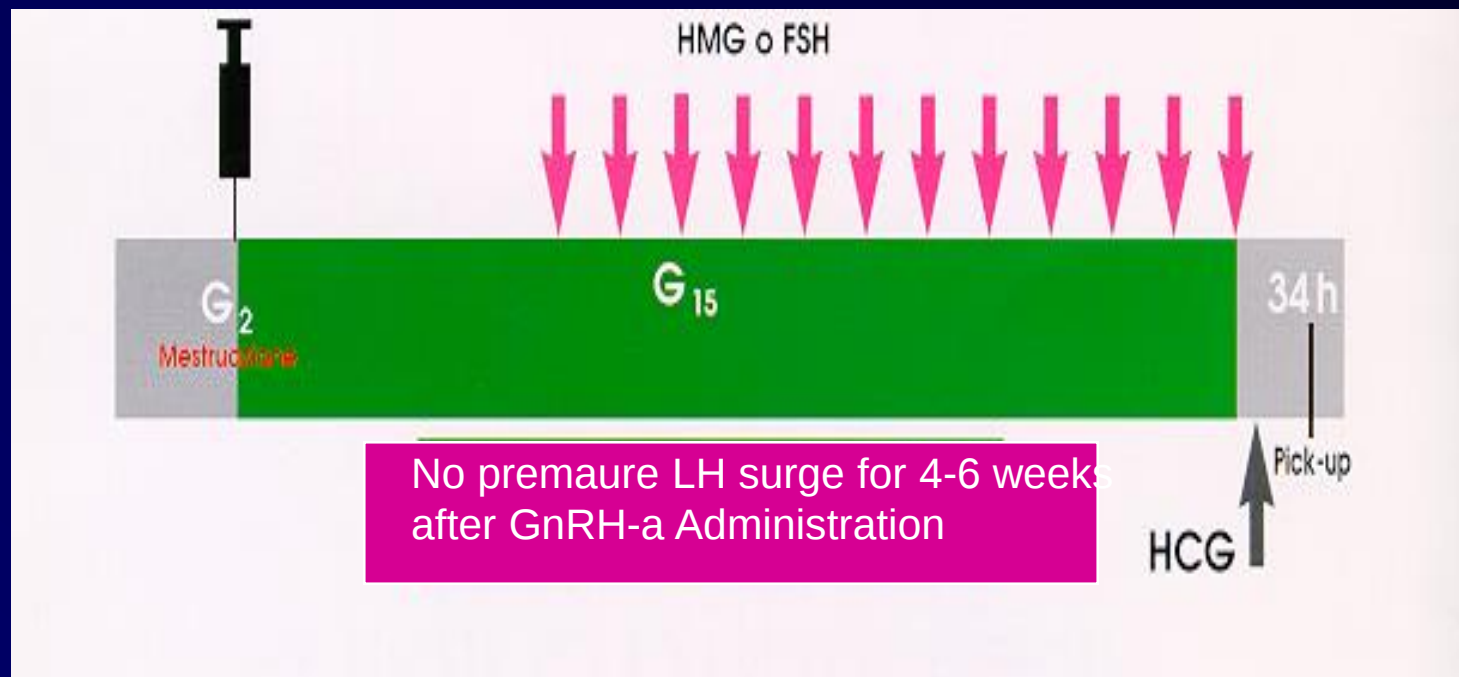


Principali schemi di utilizzo

- **Long protocol**: l'agonista del GnRH viene somministrato prima delle gonadotropine e fino alla somministrazione di hCG
- **Short protocol**: l'agonista del GnRH viene somministrato contemporaneamente alle gonadotropine e fino alla somministrazione di hCG
- **Ultra short protocol**: l'agonista del GnRH viene somministrato contemporaneamente alle gonadotropine solo per 3 giorni

Long protocol GnRH-a Depot formulation (Standard Long Protocol)

La stimolazione ovarica parte circa 15 giorni dopo la somministrazione del GnRh-a



Short protocol

GnRH-a depot or daily start with gonadotrophin administration
(D2 of menstrual period)

FORMULAZIONE DEPOT



FORMULAZIONE DAILY



Long protocol GnRH-a daily formulation

La stimolazione ovarica parte circa 15 giorni dopo l'inizio della somministrazione di GnRH-a (da D2 del periodo mestruale)

