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Ovarian stimulation for assisted reproduction technology

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History of ovarian stimulation

- 1970 Clomifen
hMG
- 1980 GnRH-agonist / hMG
- 1990 recFSH / hMG
GnRH-antagonist / hMG or recFSH

Aim of ovarian stimulation for ART

simple: soft stimulation

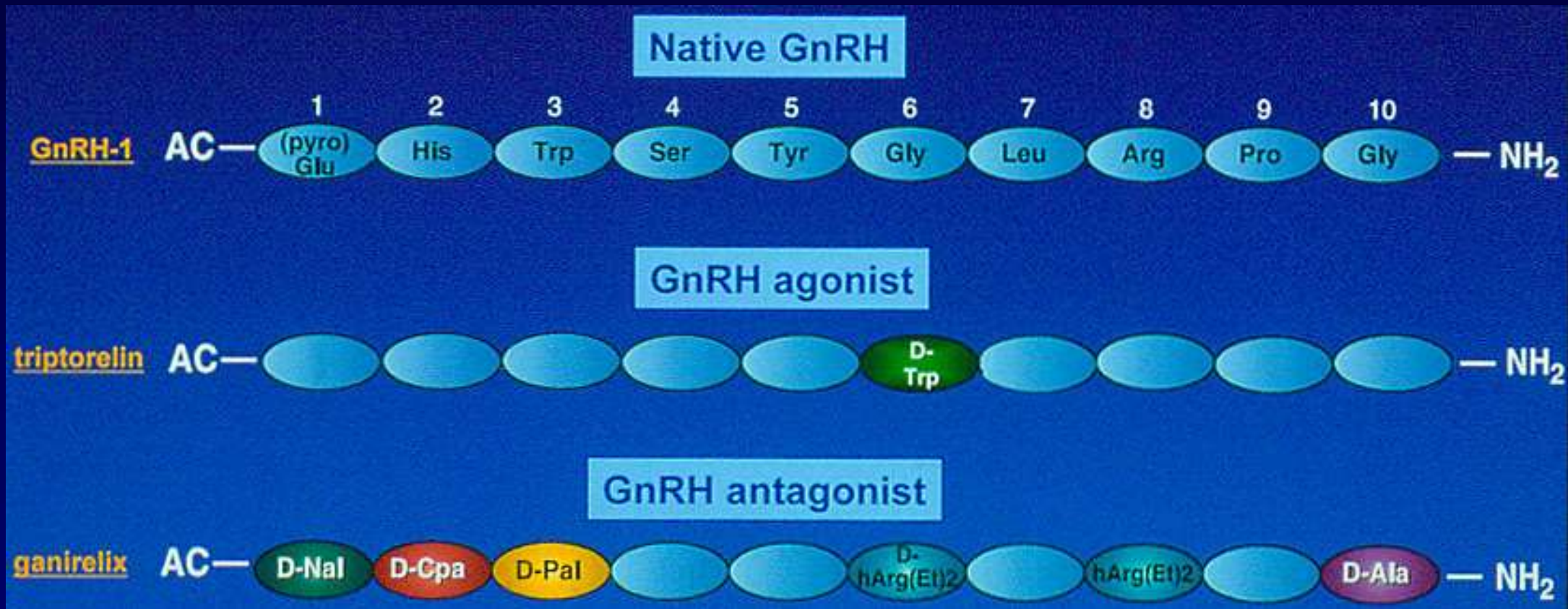
safe: less ovarian hyperstimulation syndromes

comfortable: less multiples

successful: high pregnancy rates

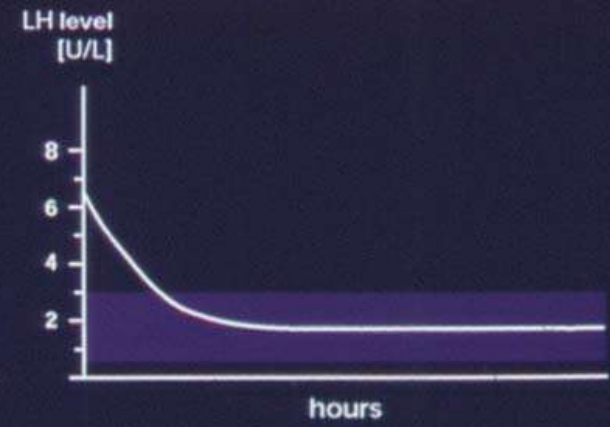
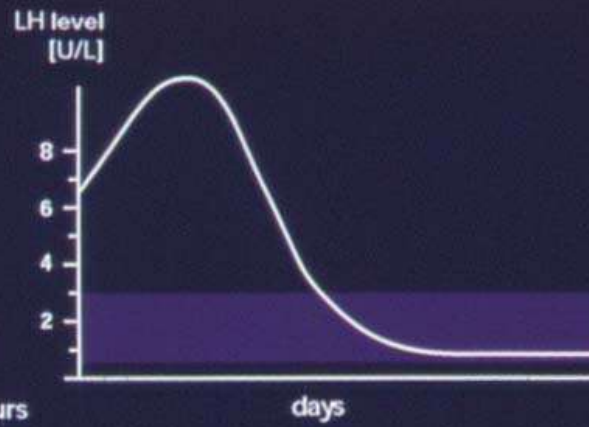
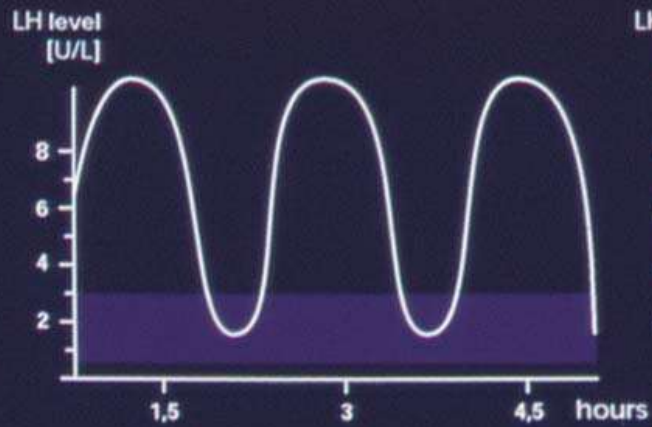
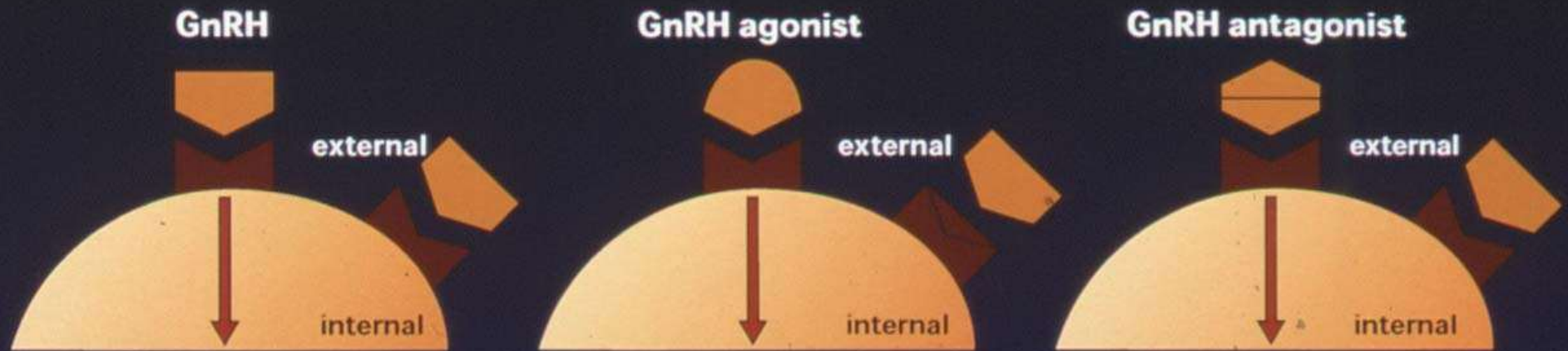
cheap: most difficult point

Structure of GnRH and analogues



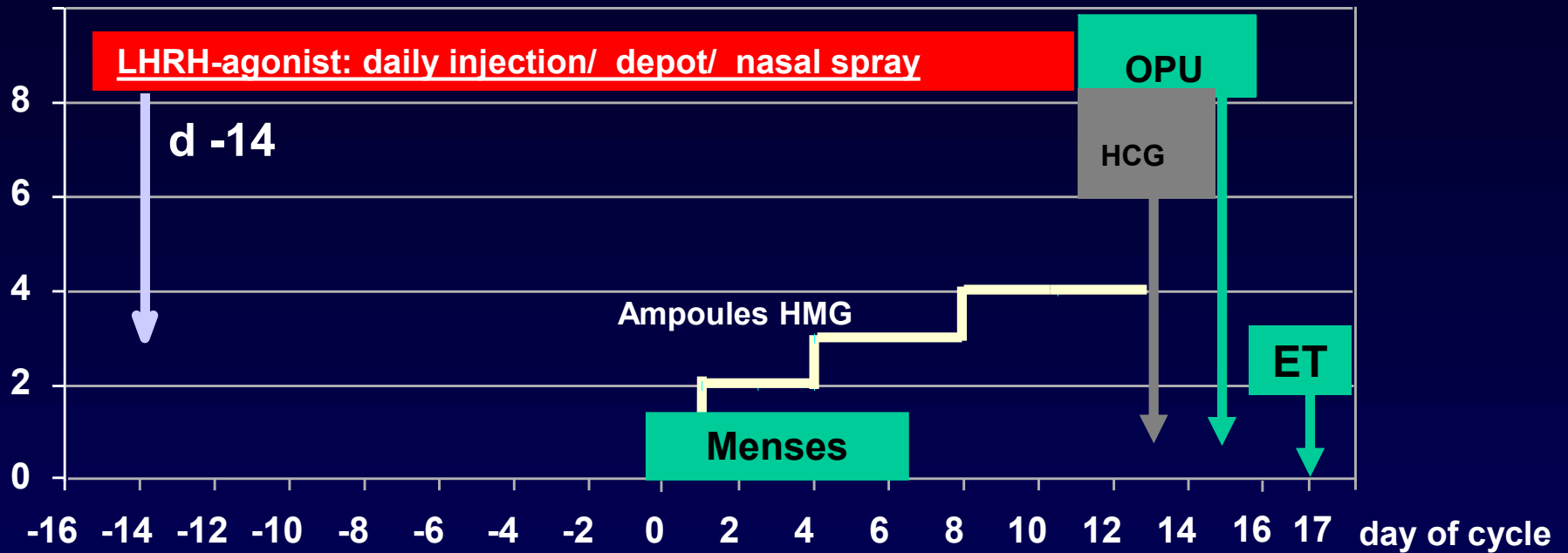
mode of action

agonist - antagonist

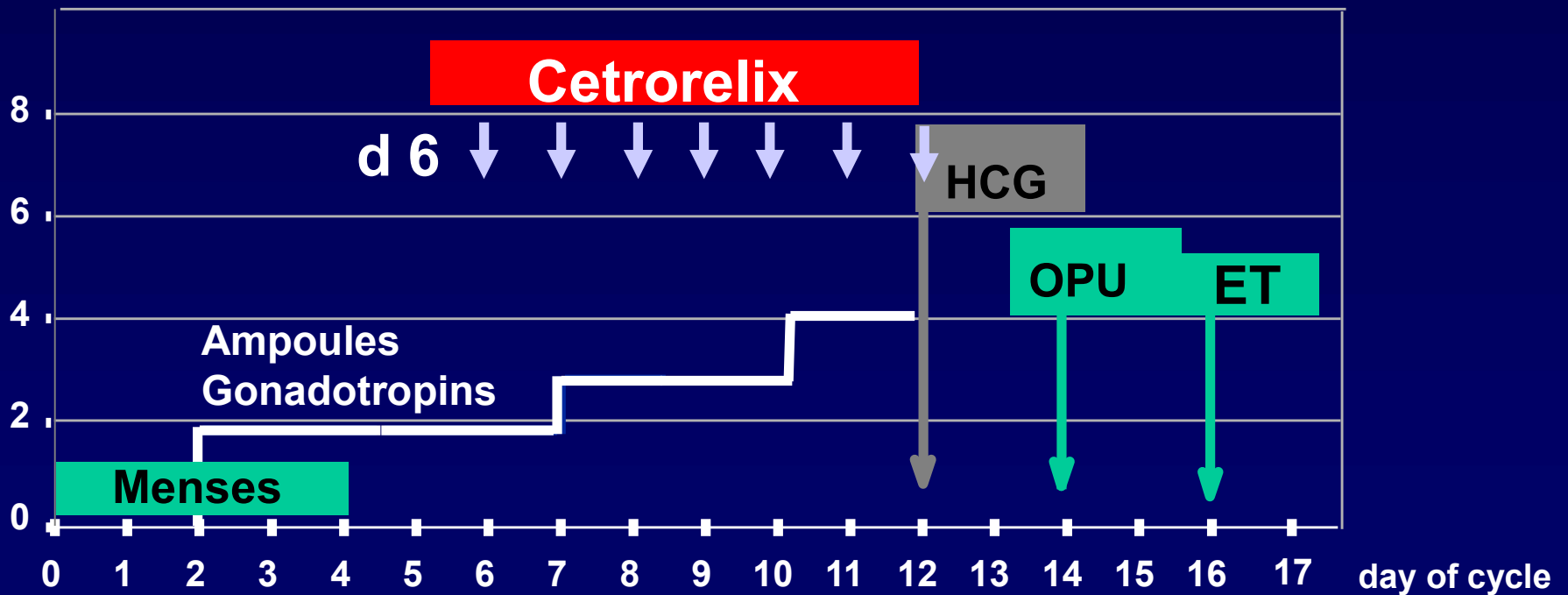


GnRH-agonist and antagonist protocol

„long protocol“



Cetrotide™
protocol

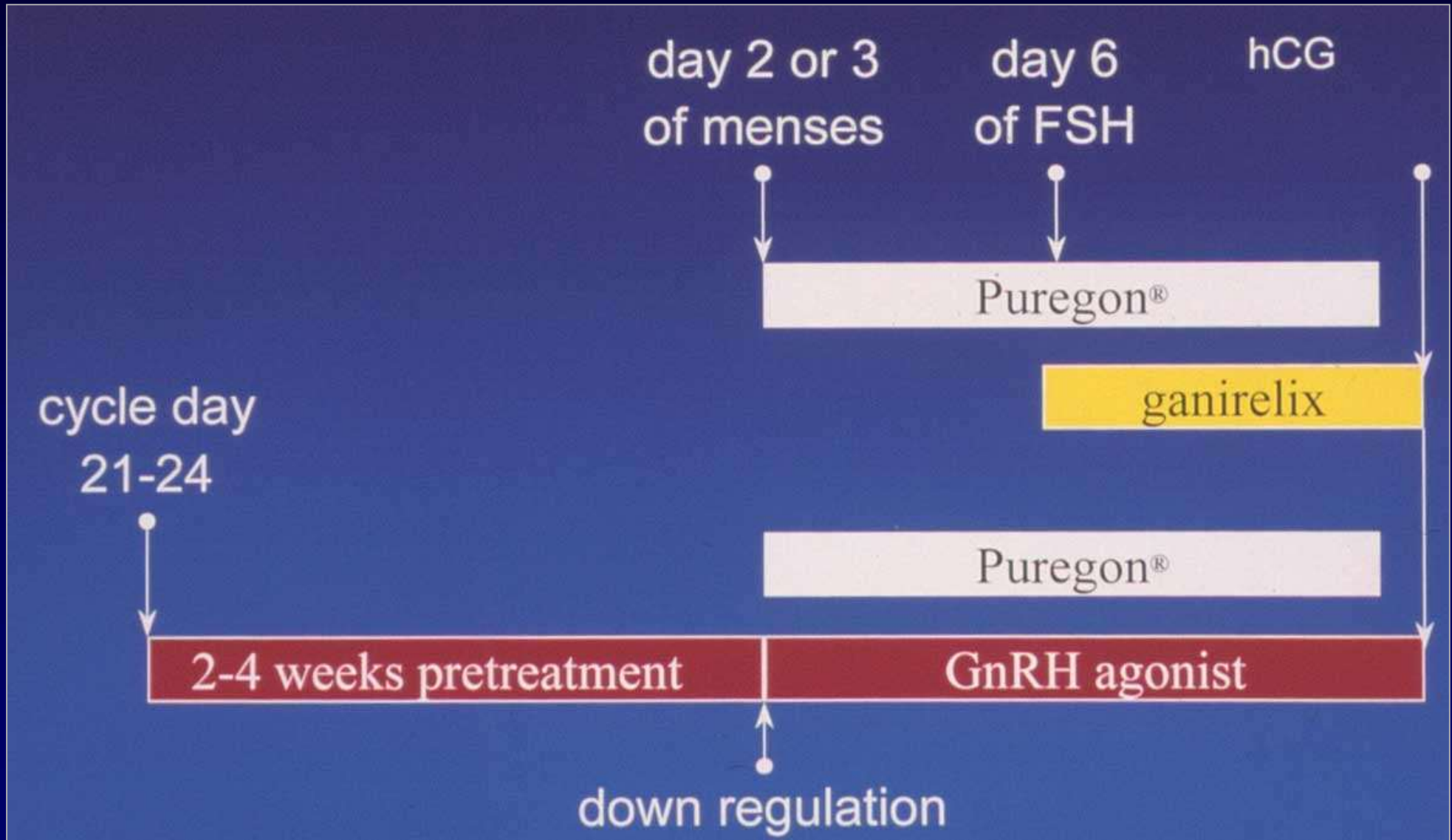


Pro- and controversies

Point to discuss

- Follicle growth and estradiol levels
- Number of follicles
- Duration of treatment and drug exposure
- Oocyte pickup and embryo transfer
- Embryo quality
- Clinical outcome: implantation, pregnancy rate and live birth rate

Treatment regimen: Ganirelix vs. GnRH-a

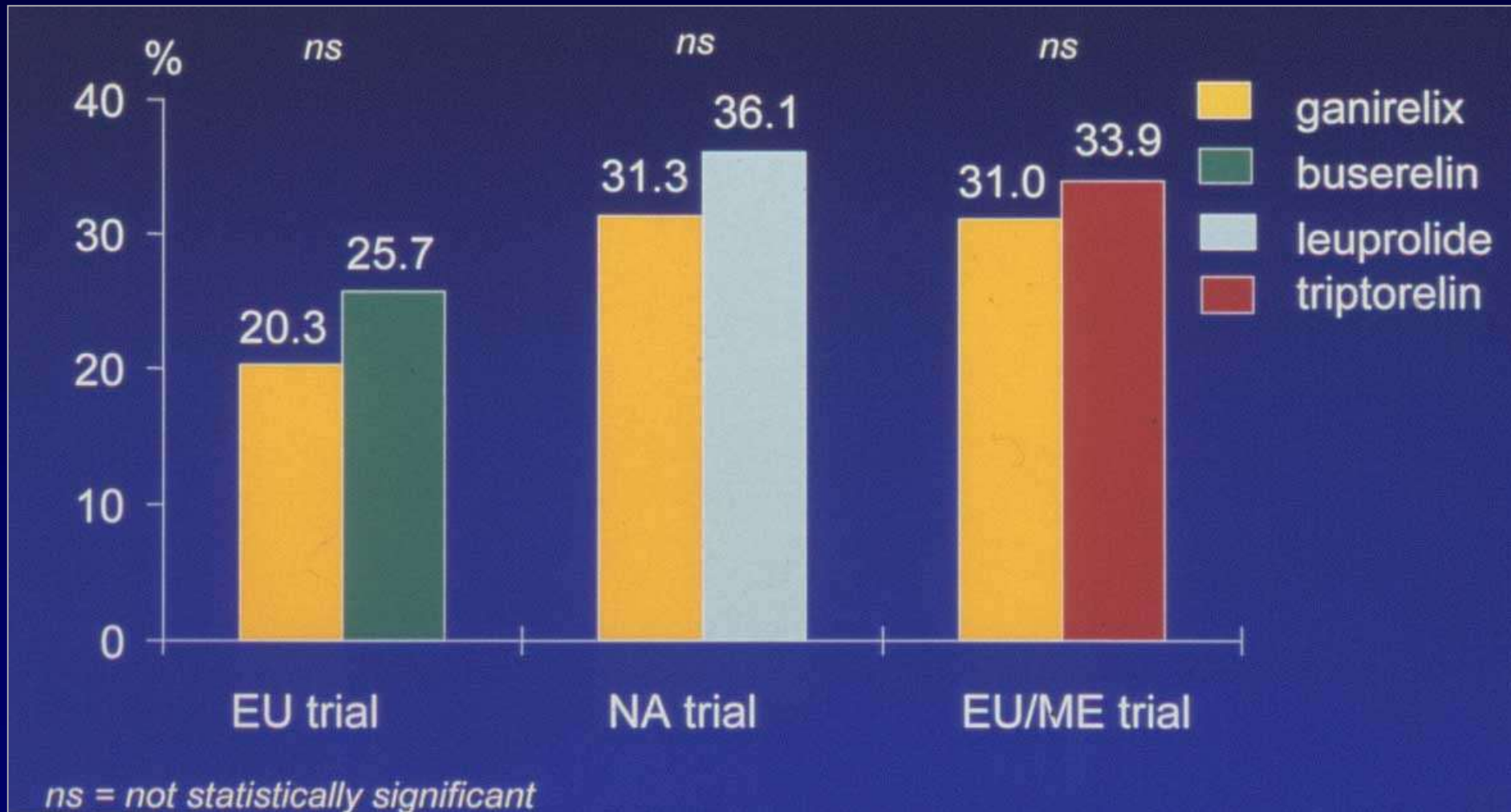


Results of these studies

Ganirelix vs GnRH-ag

- shorter stimulation
- less rec. FSH
- lower E₂ levels
- same number of good quality embryos

Ongoing pregnancy rate phase III trials per started cycle



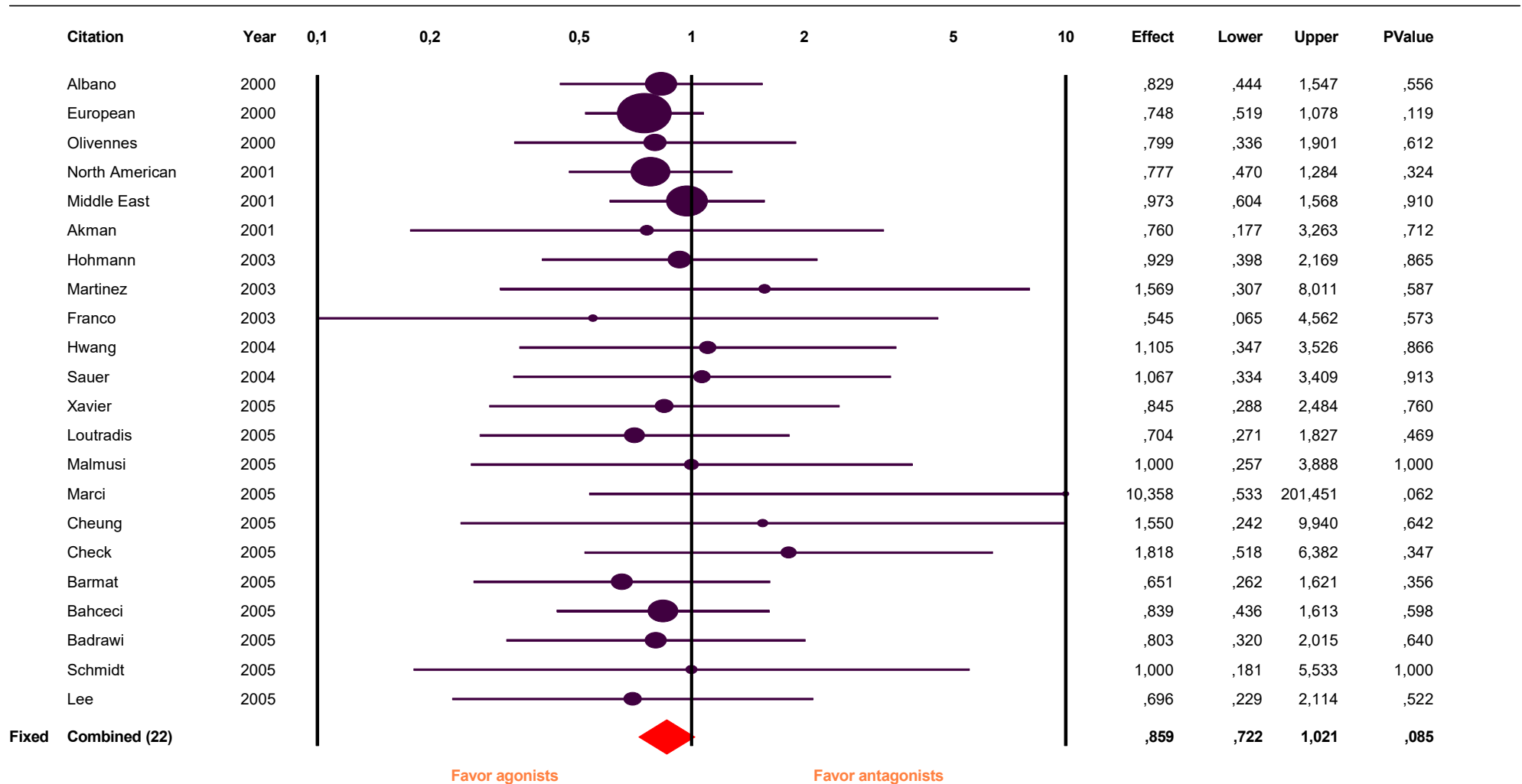
Does the probability of live birth after ovarian stimulation and IVF depend on the type of GnRH-analogue used?

A systematic review and meta-analysis

G Griesinger, J Collins, B Tarlatzis,
P Devroey, K Diedrich, EM Kolibianakis



LIVE BIRTH



Odds ratio:0.859

p=0.085

Rate difference

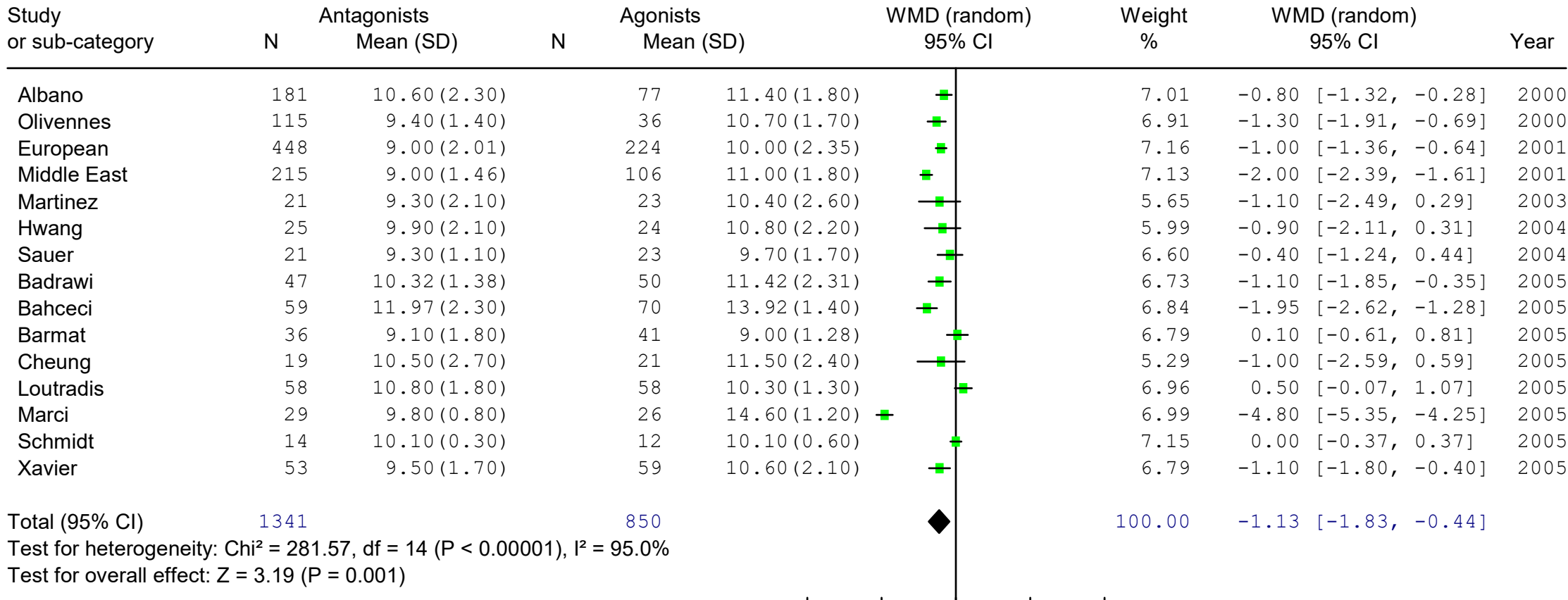
2.7%

Duration of FSH treatment

Review: GnRH Antagonists vs. GnRH agonists

Comparison: 05 Duration of stimulation

Outcome: 01 Duration of stimulation



-10 -5 0 5 10

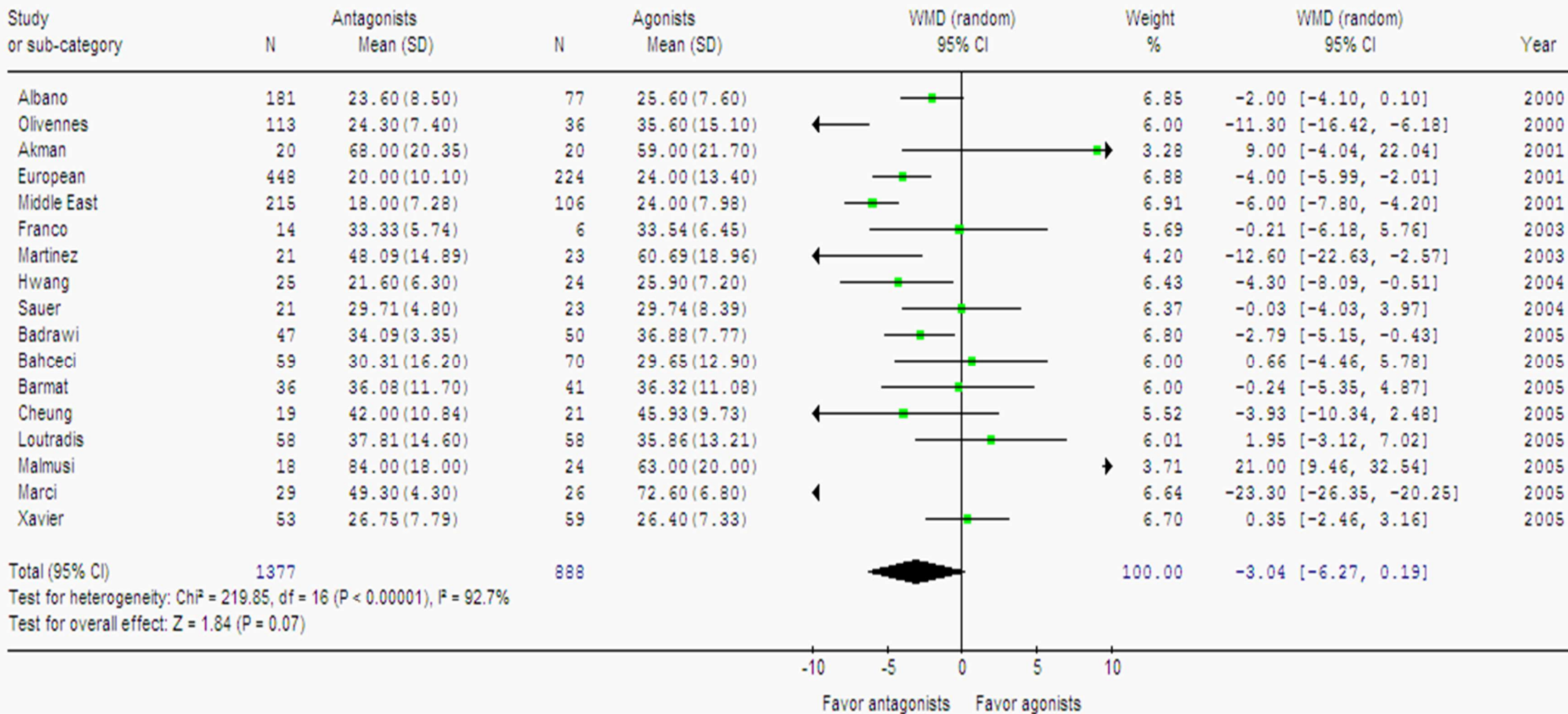
Favor antagonists Favor agonists

1.1 less days with antagonists

p<0.001

FSH requirement

Review: GnRH Antagonists vs. GnRH agonists
 Comparison: 04 FSH ampoules
 Outcome: 01 FSH ampoules required

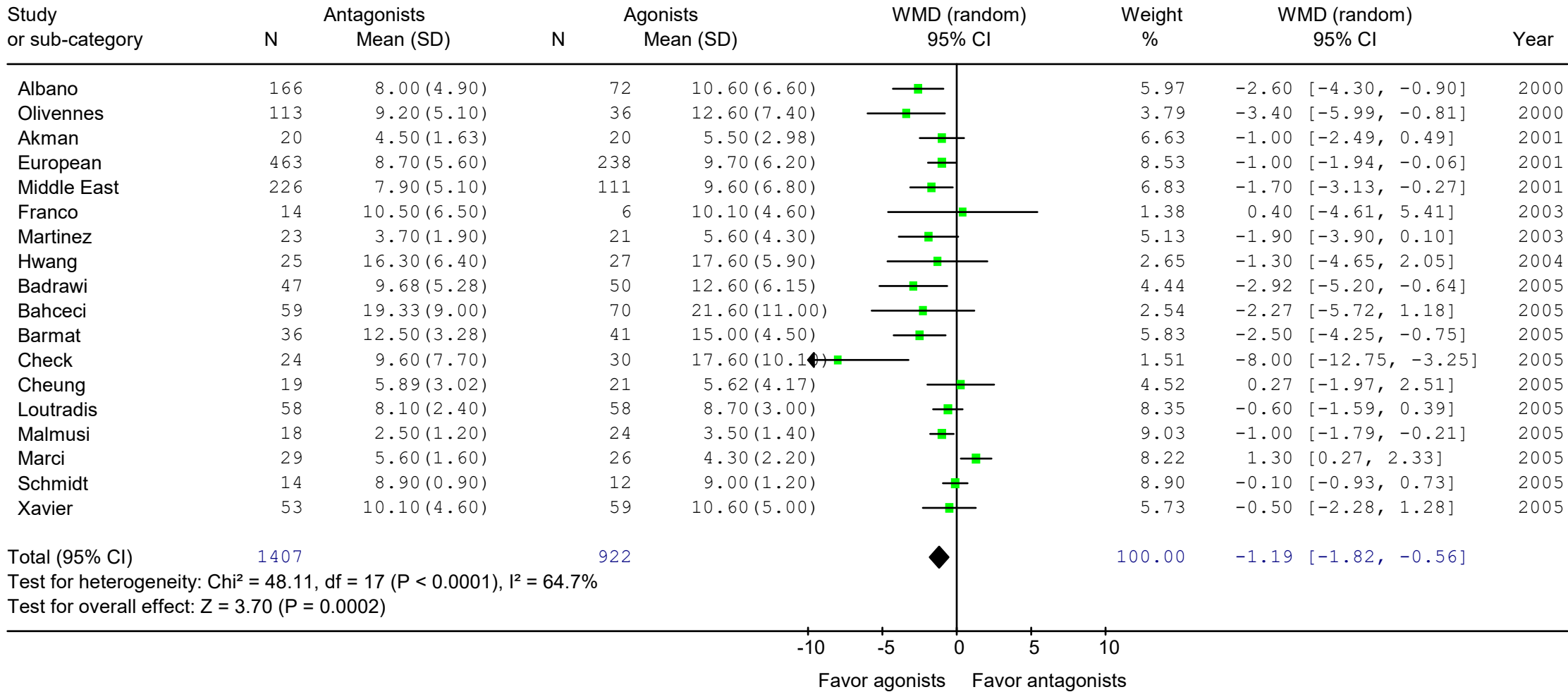


3.0 ampoules less with GnRH antagonists

p<0.07

COCs retrieved

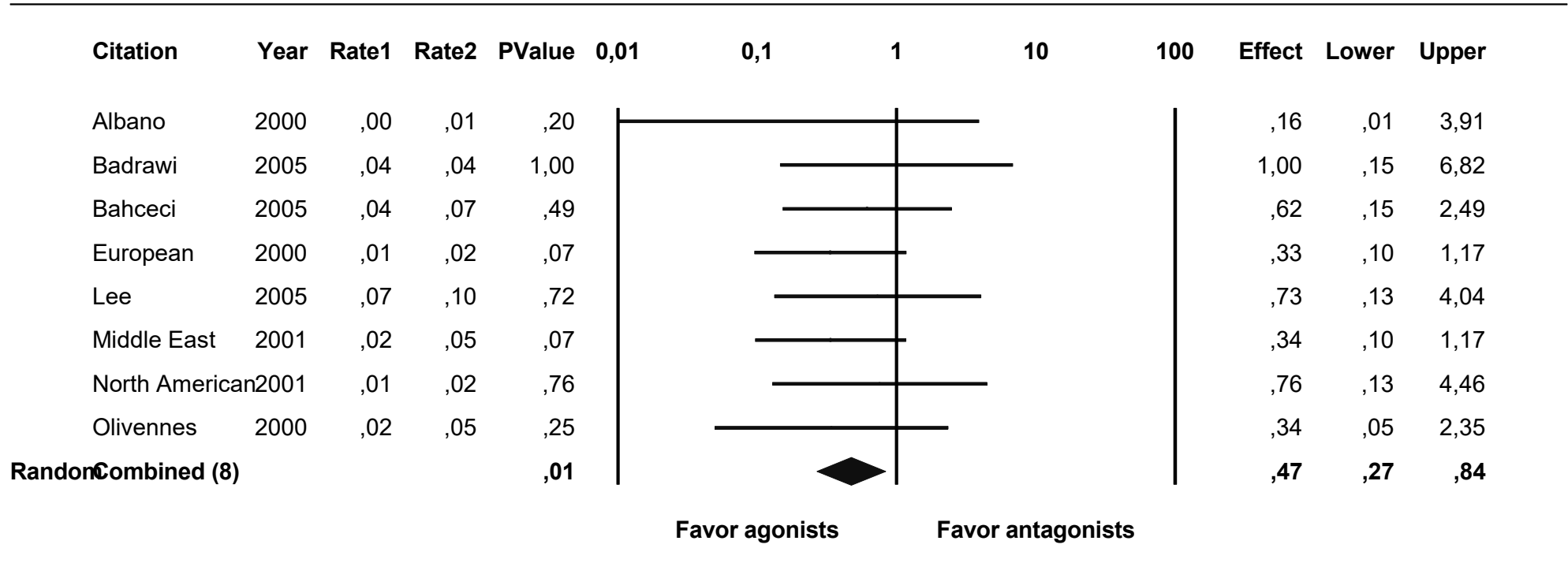
Review: GnRH Antagonists vs. GnRH agonists
 Comparison: 02 COCs
 Outcome: 01 COCs retrieved



1.2 COCs more with GnRH agonists

p<0.001

Hospital admission due to OHSS



RR : 0.47

~ 2 times less risk to be admitted due to OHSS with GnRH antagonists

Summary I

- **Advantages of GnRH-antagonists**
 - simple stimulation
 - fixed initiation of GnRH-antagonist on day 6
 - no LH supplementation
 - no increase of gonadotrophin dose at GnRH-antagonist initiation
 - ovulation induction for ART by dominant follicle of $\geq 17\text{mm}$
 - luteal phase supplementation is mandatory

Summary II

- **Advantages of GnRH-antagonists**
 - fits into the normal cycle
(„the patients like it“)
 - less side effects in comparison to the long protocol:
 1. Ø cysts
 2. Ø hormonal withdrawal
 3. less OHSS
 - **no significant difference in the probability of live birth between GnRH-agonists and antagonists**

Important points for ovarian stimulation with gonadotrophins + GnRH-antag.

- low progesterone at the beginning of stimulation
- LH level on day 8 should be low (< 1.0 IU/l)
- Endometrial advancement ≤ 3 days
- Early hCG administration (≥ 3 follicles ≥ 17 mm)

New protocols in ovarian stimulation with GnRH-antagonists

- individualization of the stimulation
- „soft protocols“
- oral contraceptives

Oral contraceptives data

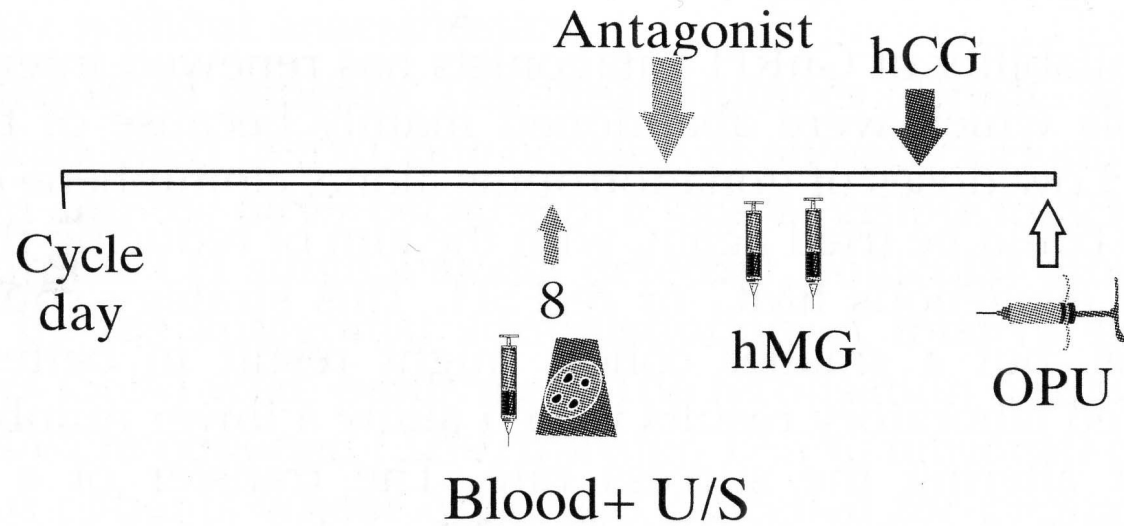
	with OCs (n = 136)	without OCs (n = 86)
pregnancy per ET	41.7%	41.4%
pregnancy per attempt	33.1%	33.7%
implantation rate	18.7%	21.2%

- **no difference in ovarian response and outcome**
- **timing and scheduling easier**

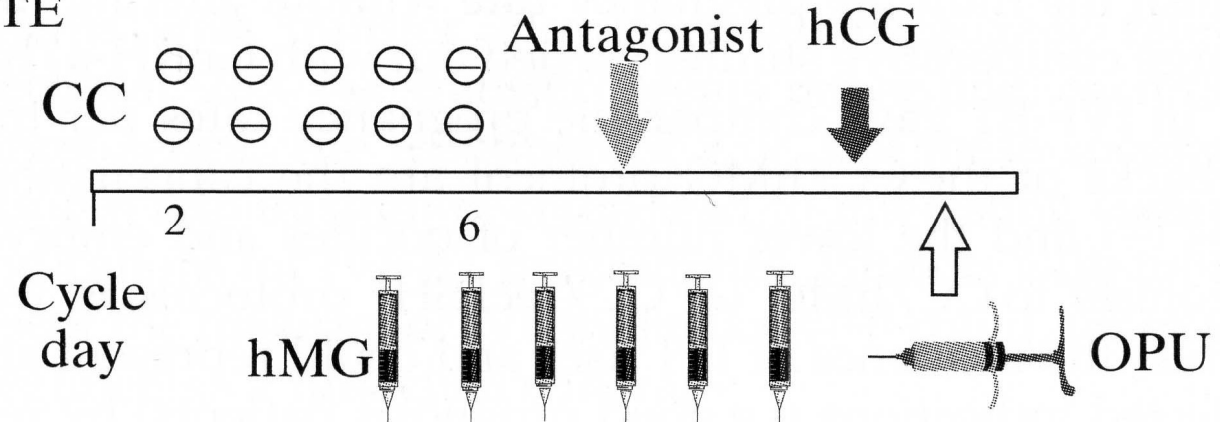
II. Simple

The soft stimulation protocols

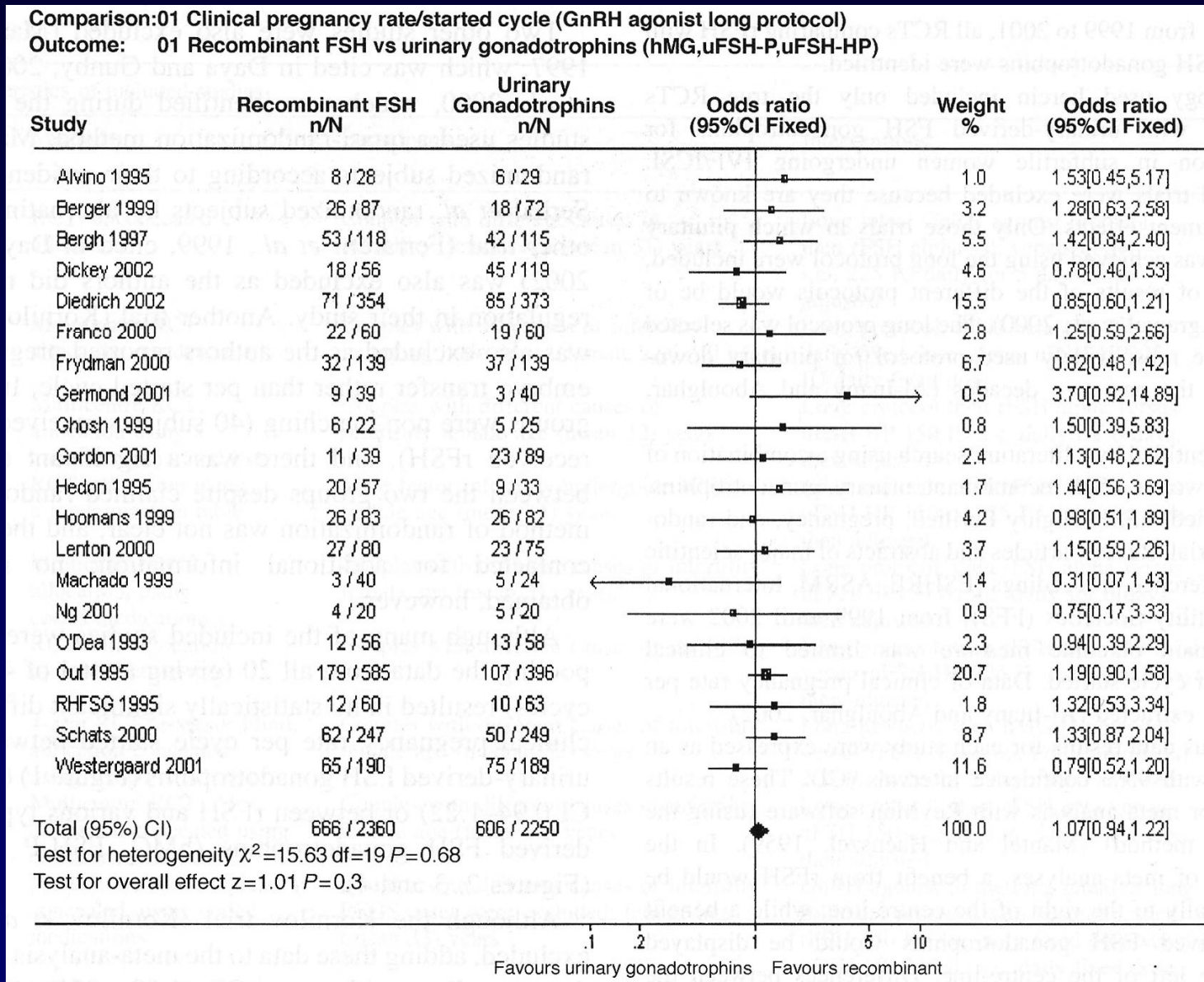
NATURAL CYCLE
AND hMG SUPPORT



CLOMIPHENE CITRATE
AND ANTAGONIST



Comparison rec FSH vs urinary gonadotrophins



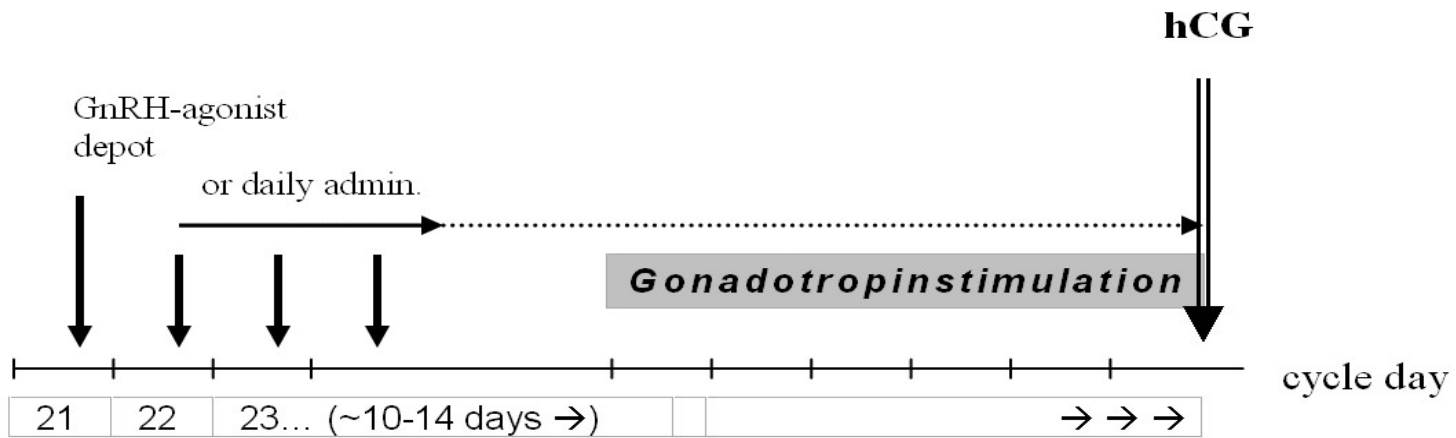


FIGURE 1A: GNRH-AGONIST, *LONG-LUTEAL* PROTOCOL

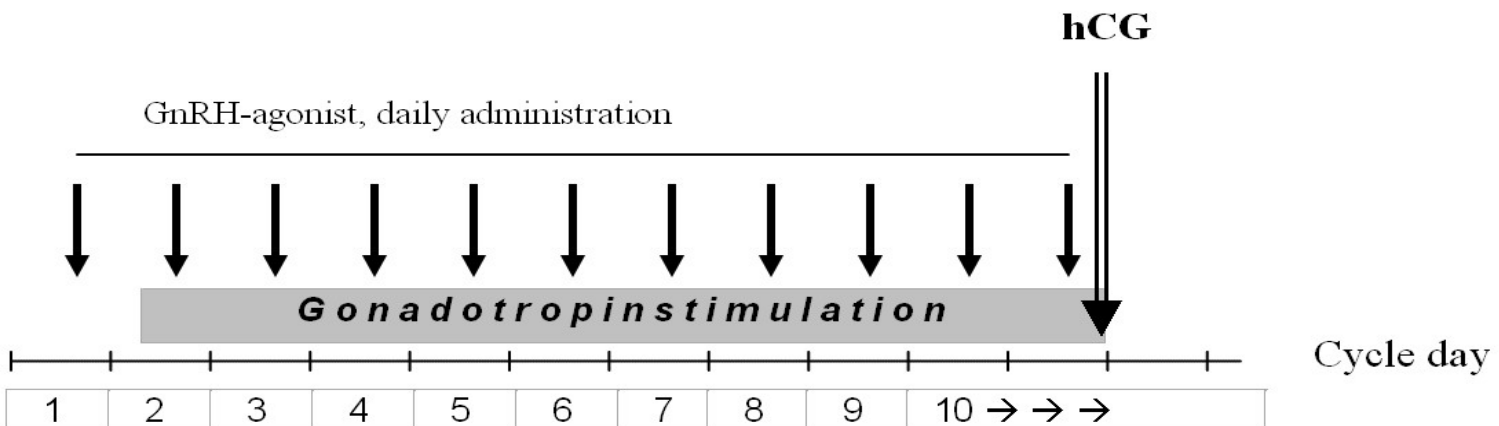
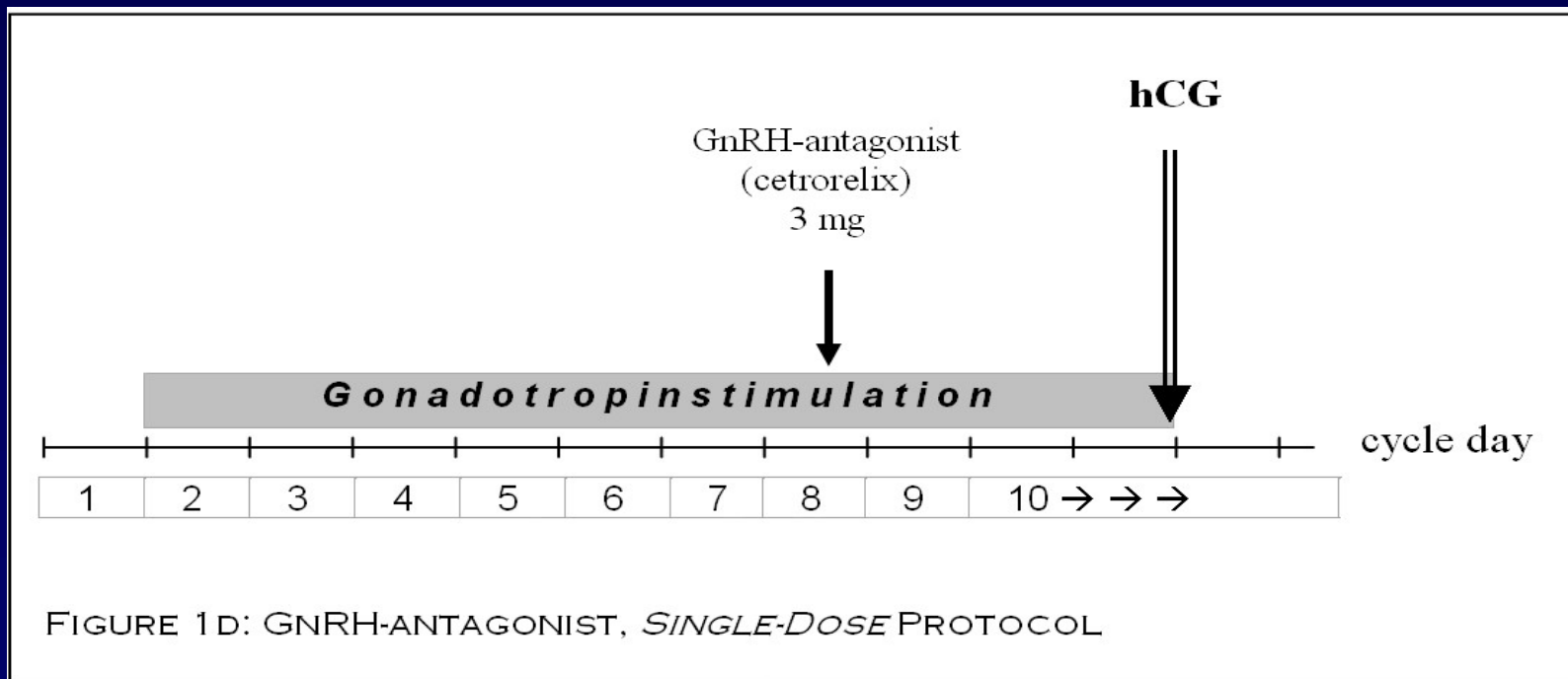
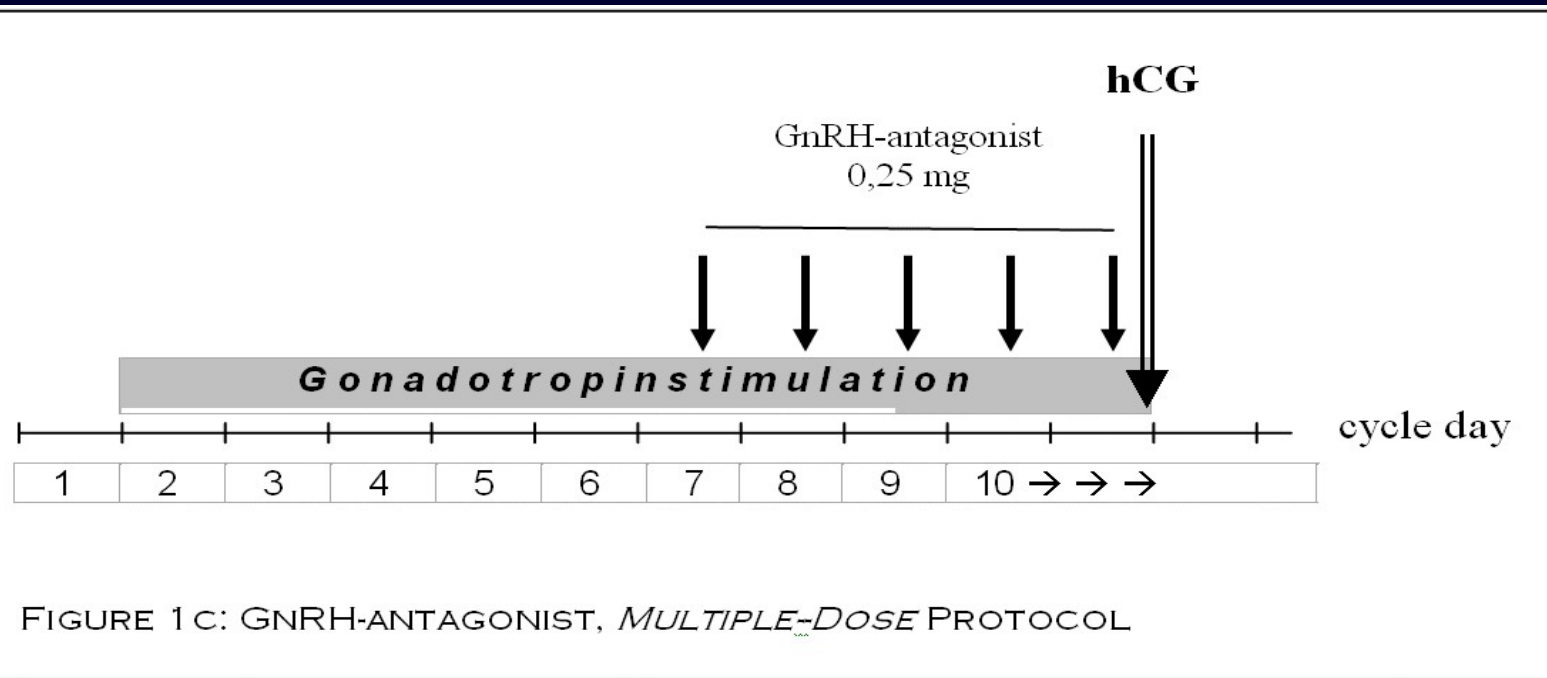
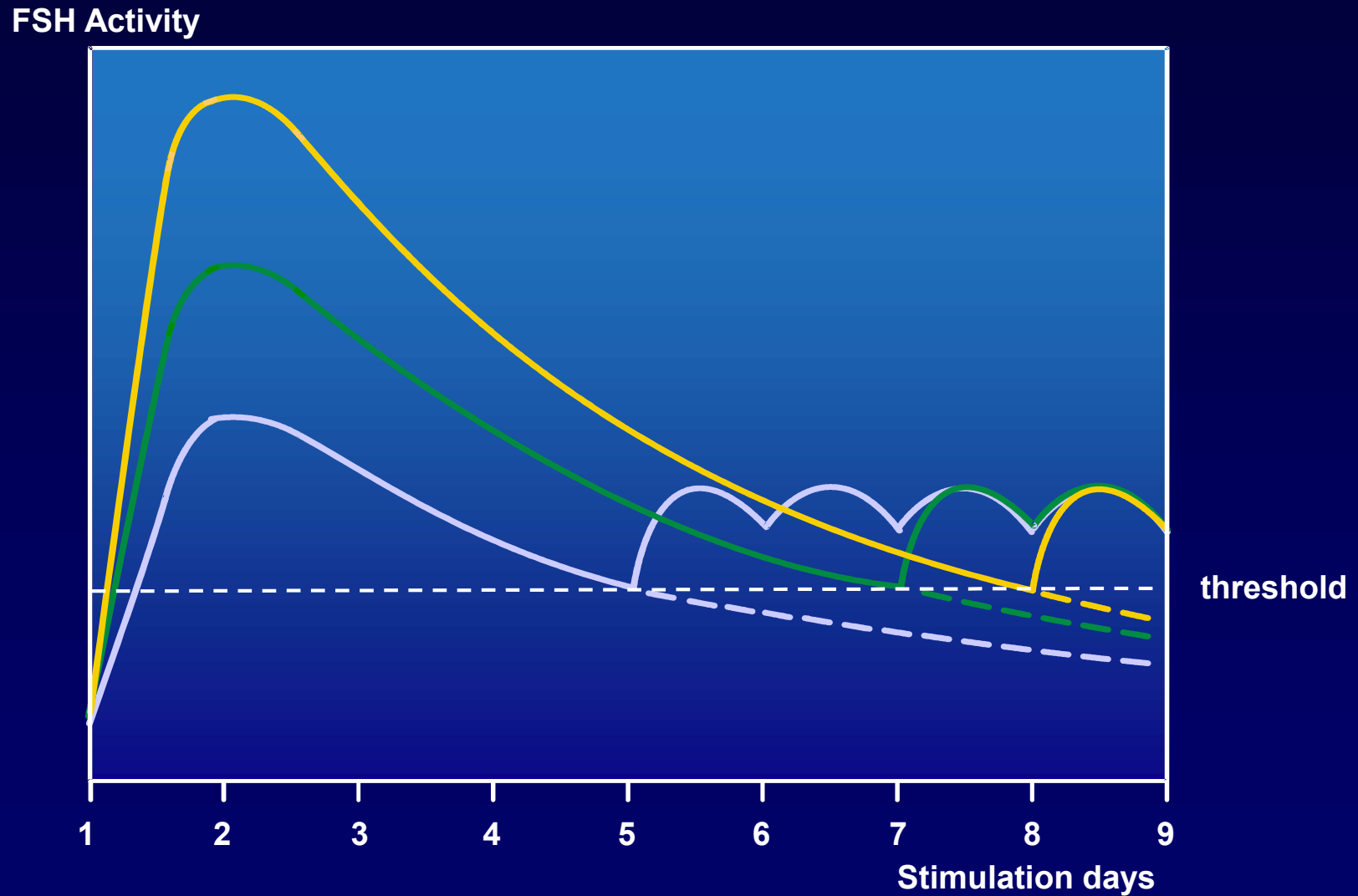


FIGURE 1B: GNRH-AGONIST, *SHORT* PROTOCOL



Induced multiple follicle growth by long-acting recFSH and daily recFSH



**Start cycle day 2-3
single dose FSH-CTP**

Treatment day 8 continue Puregon

150 mcg

150 IU

*** HCG \geq 3 follicles \geq 17 mm**

**Start GnRH-antagonist
day 5 or 6**

**IVF
or
ICSI**

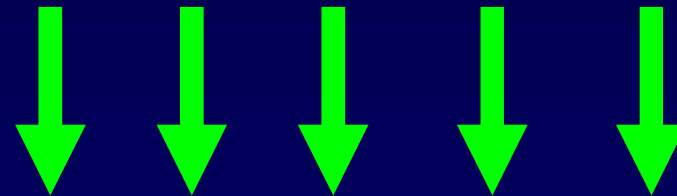
**Luteal Phase
Support**

The future of ovarian stimulation

FSH CTP s.c.



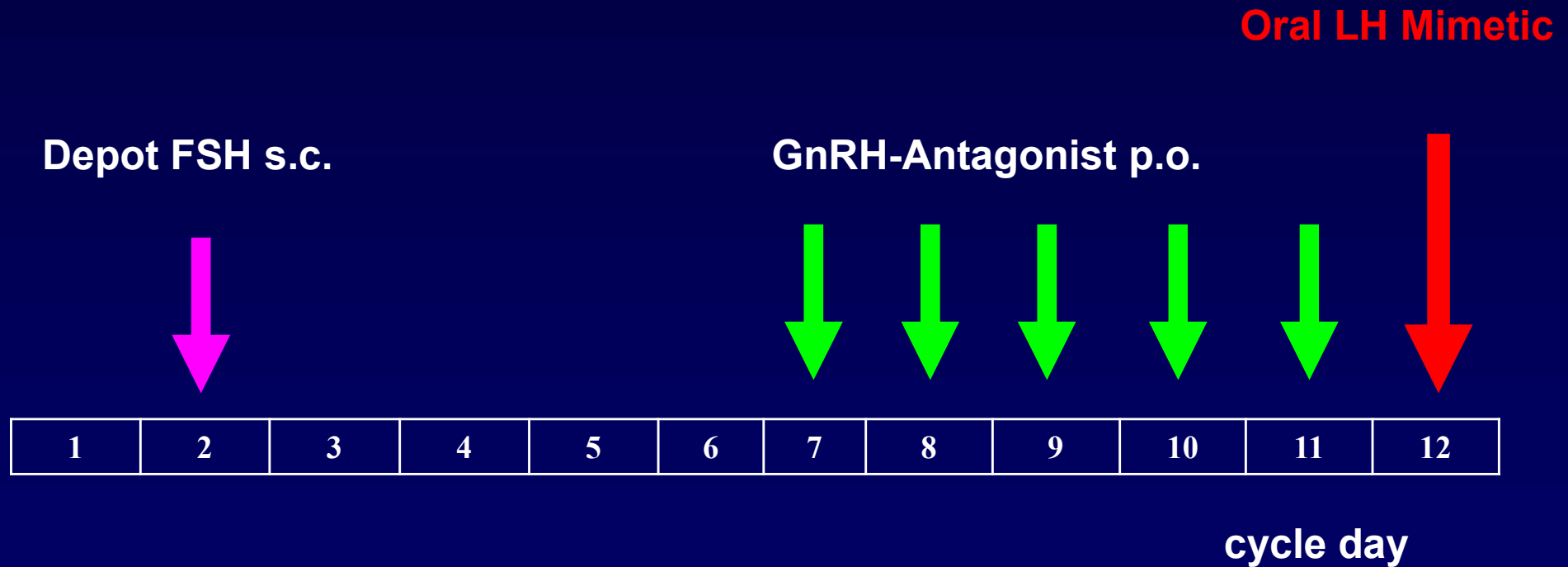
GnRH-Antagonist p.o.



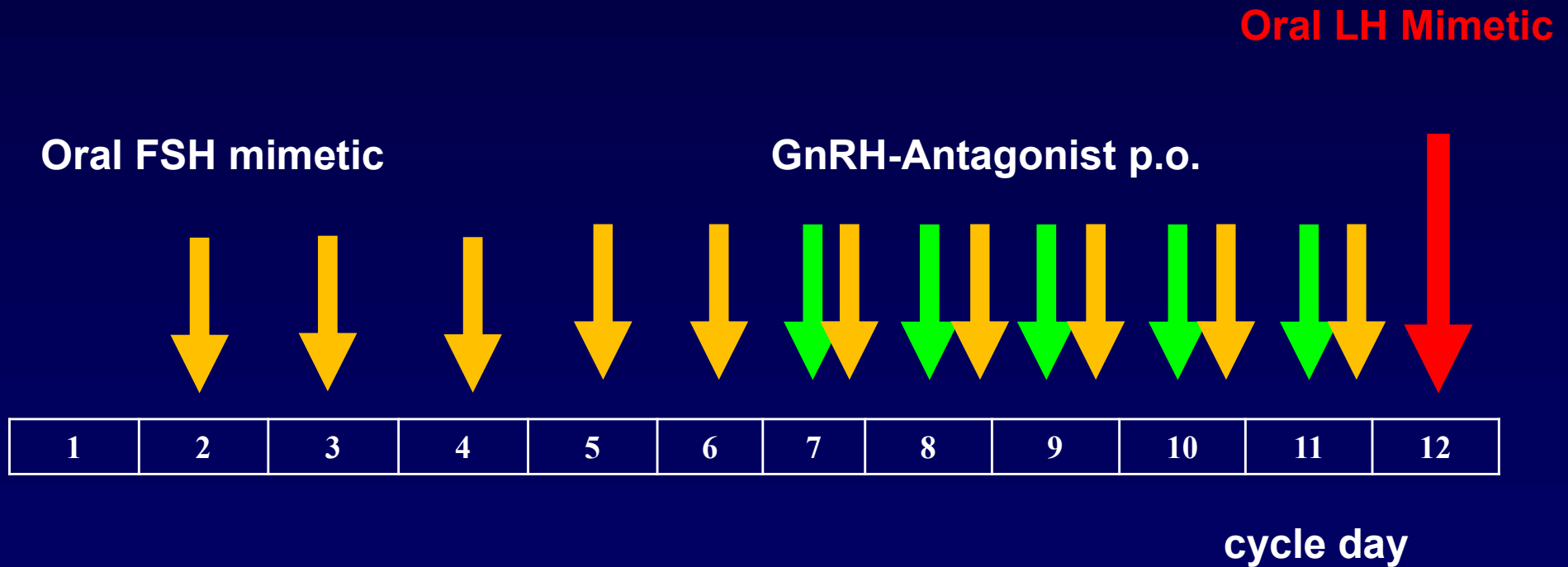
1	2	3	4	5	6	7	8	9	10	11	12
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cycle day

The future of ovarian stimulation



The future of ovarian stimulation



Ovarian stimulation in 2025

New drugs &
modified protocols

FSH-CTP

Orally active non
peptid FSH and LH

Orally active GnRH-
antagonists

Aromatase Inhibitors

In vitro maturation
without
ovarian stimulation

Oocyte/ovarian
tissue banking for all
women

In-vitro
folliculogenesis

In-vitro Maturation