

The Use of GnRH Antagonists in Gynaecology

AMR EL NOURY

Tutor

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Introduction

- (LHRH) GnRH discovery Shally 1971
- Knowledge of LH effect on pregnancy outcome and problem of premature LH surge
- GnRH agonists
 - Problems:
 - usually long duration of treatment
 - flare up effect
- GnRH - Antagonists
 - Avoid problems of GnRH agonists ?

Types of GnRH antagonists

- There are several types
- Decapeptides
- First Generation
 - (Histamine release & severe allergy)
- Second generation
 - (allergy and gel formation)
- Third Generation
 - (well tolerated)
 - Cetrorelix (Asta Medica) Market
 - Ganirelix (Organon) approval

Hexapeptides, Heptapetides

Decapeptide

1 2 3 4 5 6 7 8 9 10



GnRH



GnRH Agonists



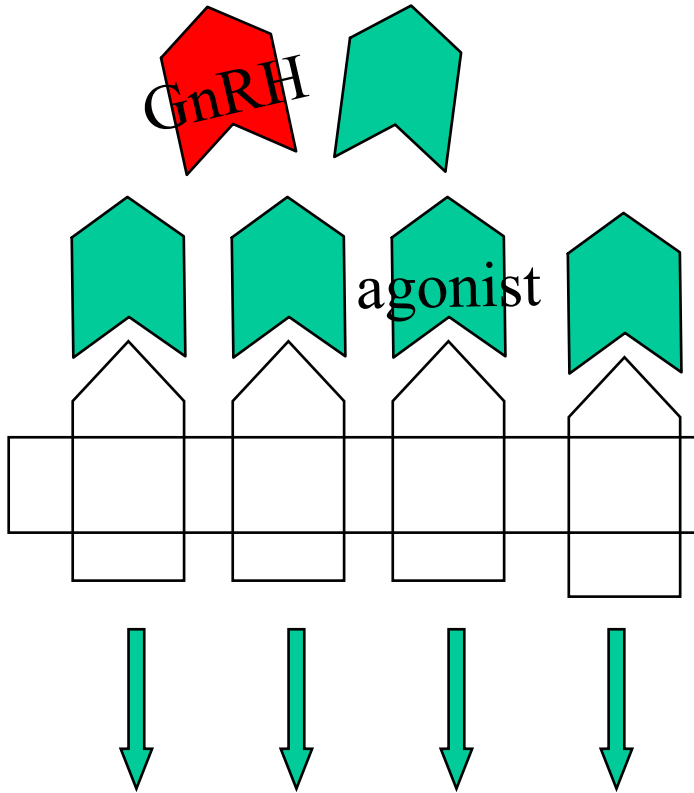
GnRH Antagonists

Cetrorelix

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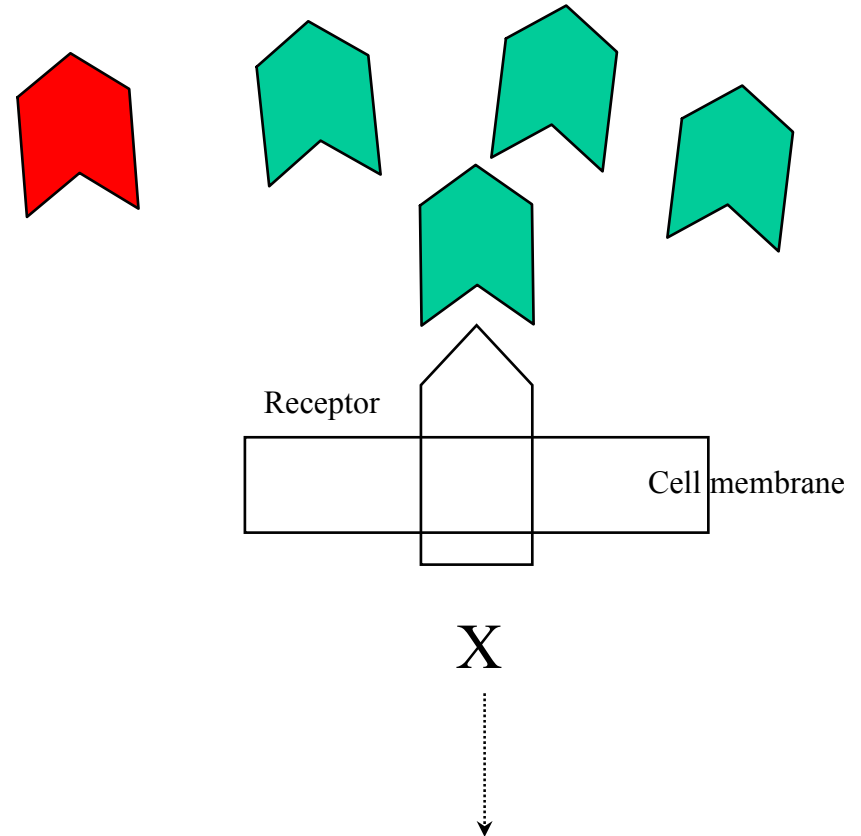
Mode of Action: GnRH Agonists

GnRH Agonist-Initial phase:
stimulation



Increased LH/FSH
initial flare up

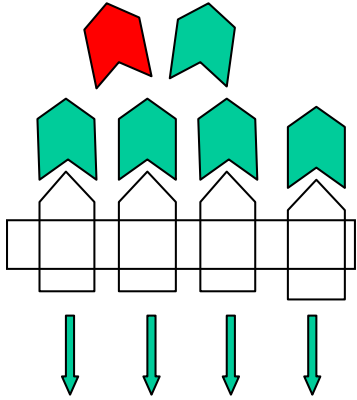
GnRH Agonist-chronic administration
/ suppression



Loss of receptors (down regulation)
native GnRH excluded from receptor
binding (desensitization)

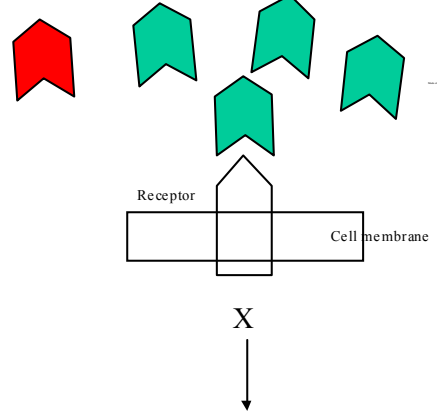
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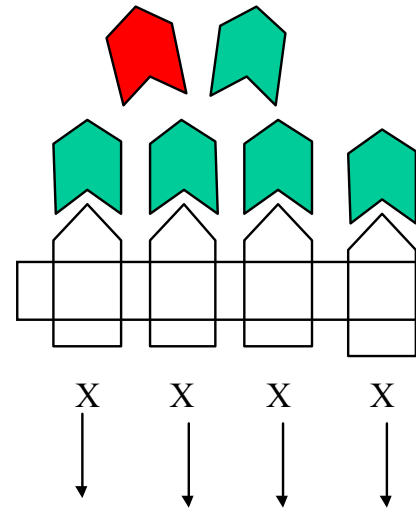
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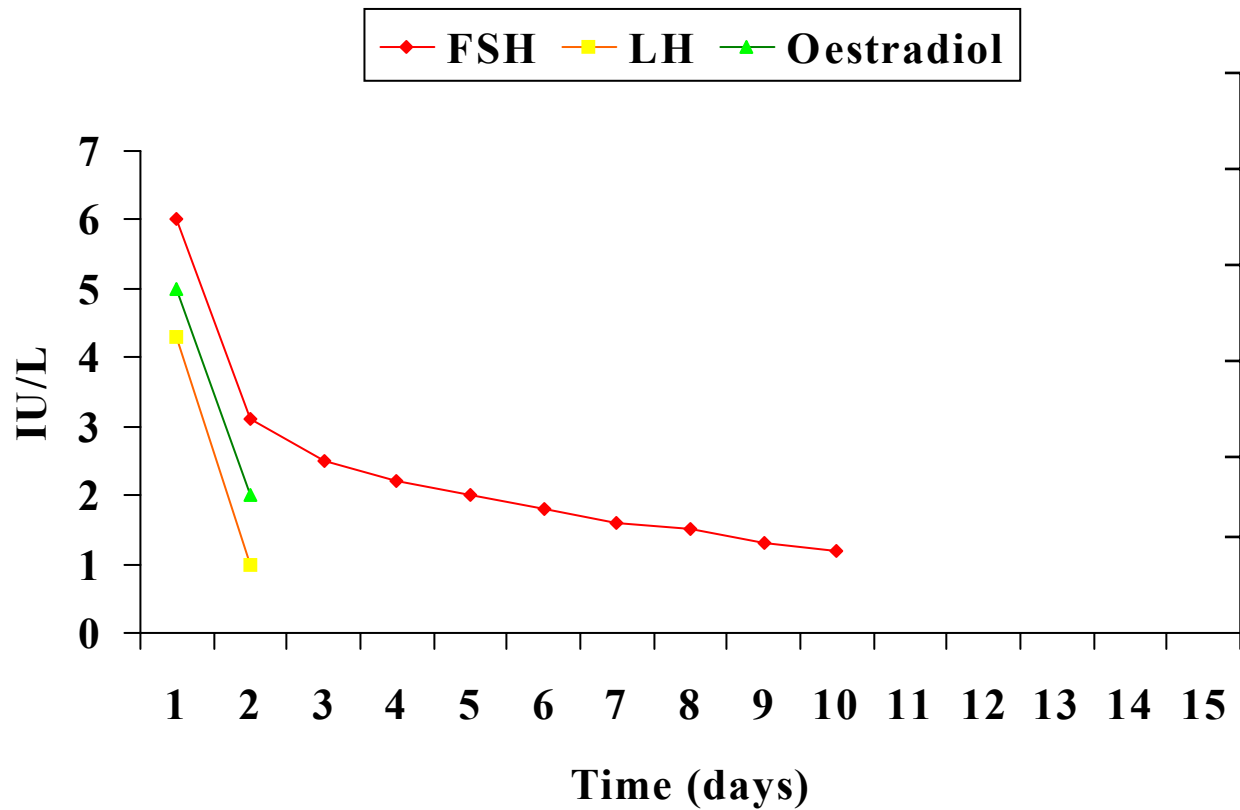
Competitive binding



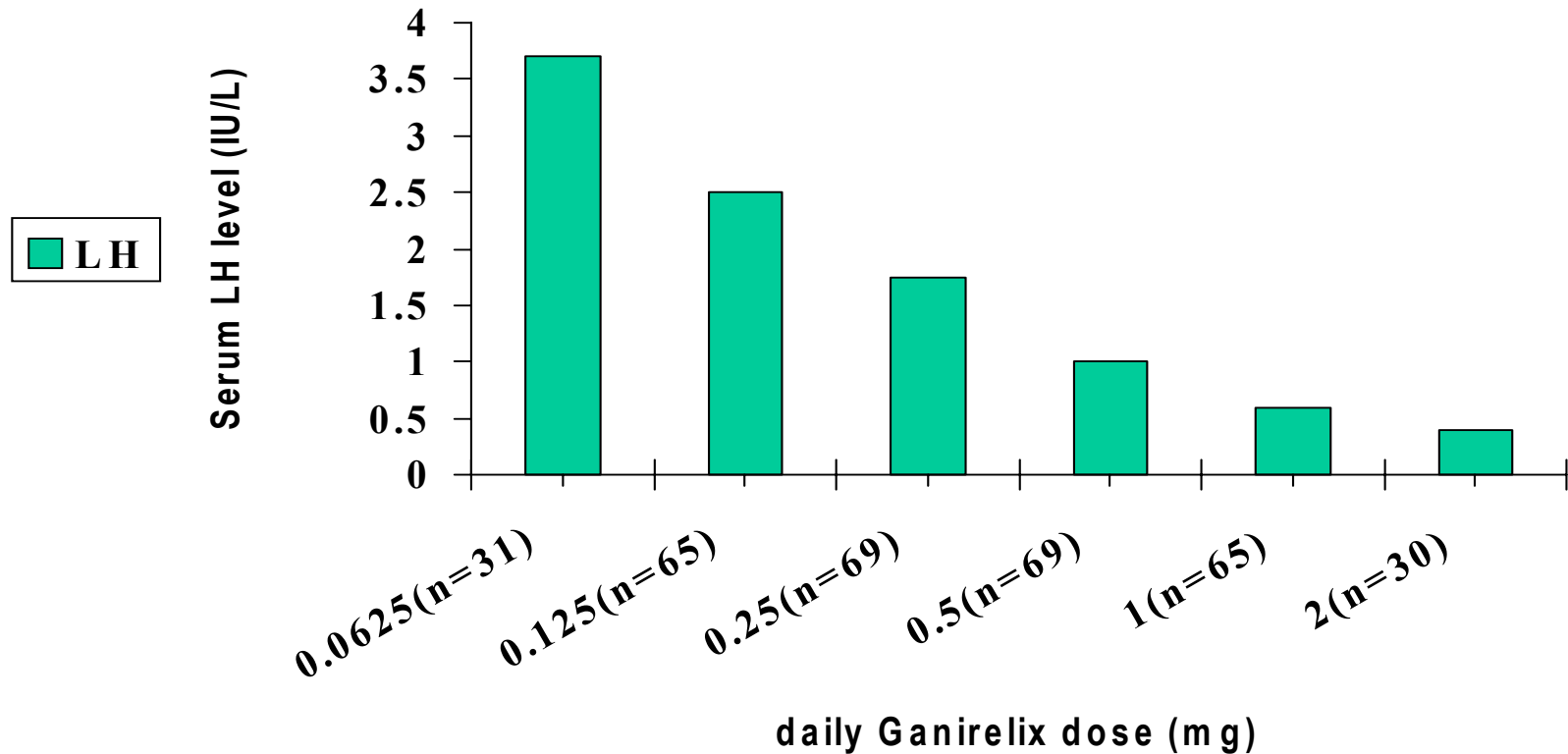
Immediate decrease in
LH , FSH

No initial flare up

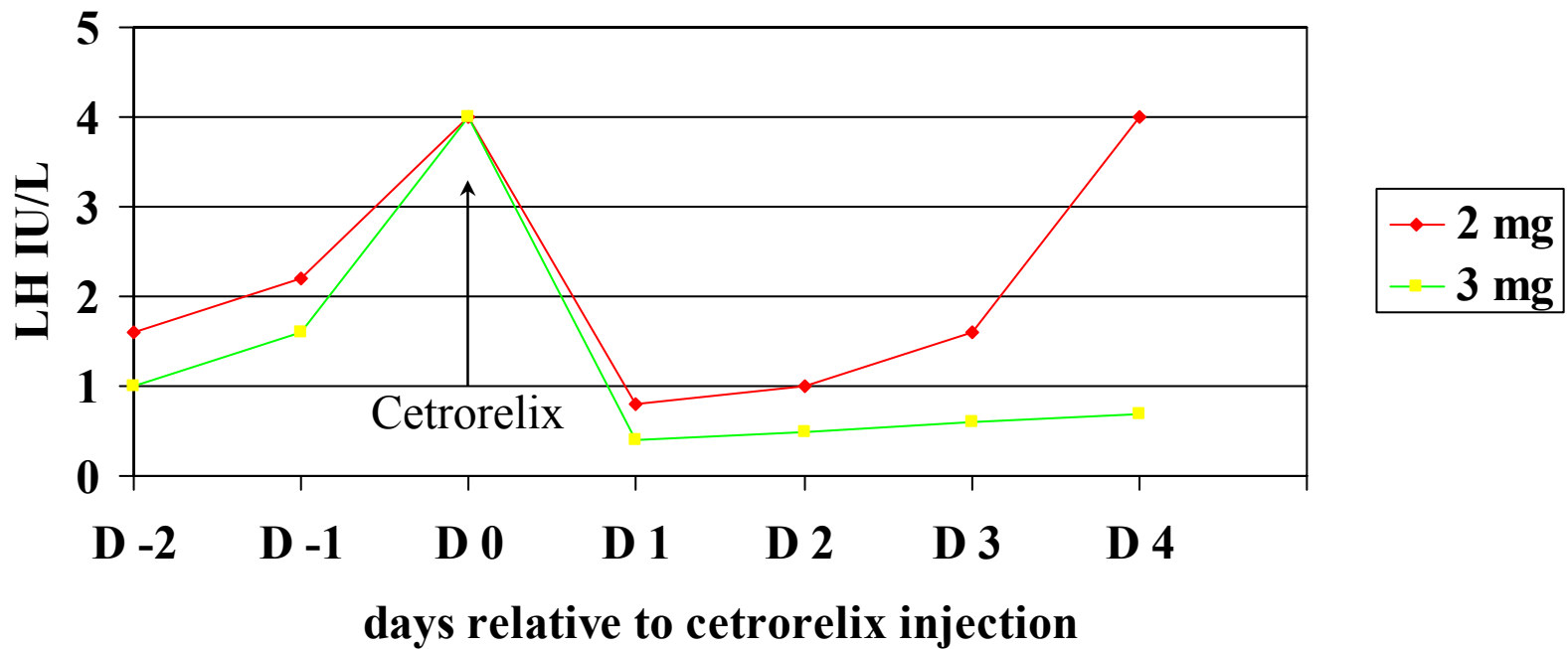
Median serum hormone concentration during Ganirelix treatment



Effect of different doses of Ganirelix on serum LH



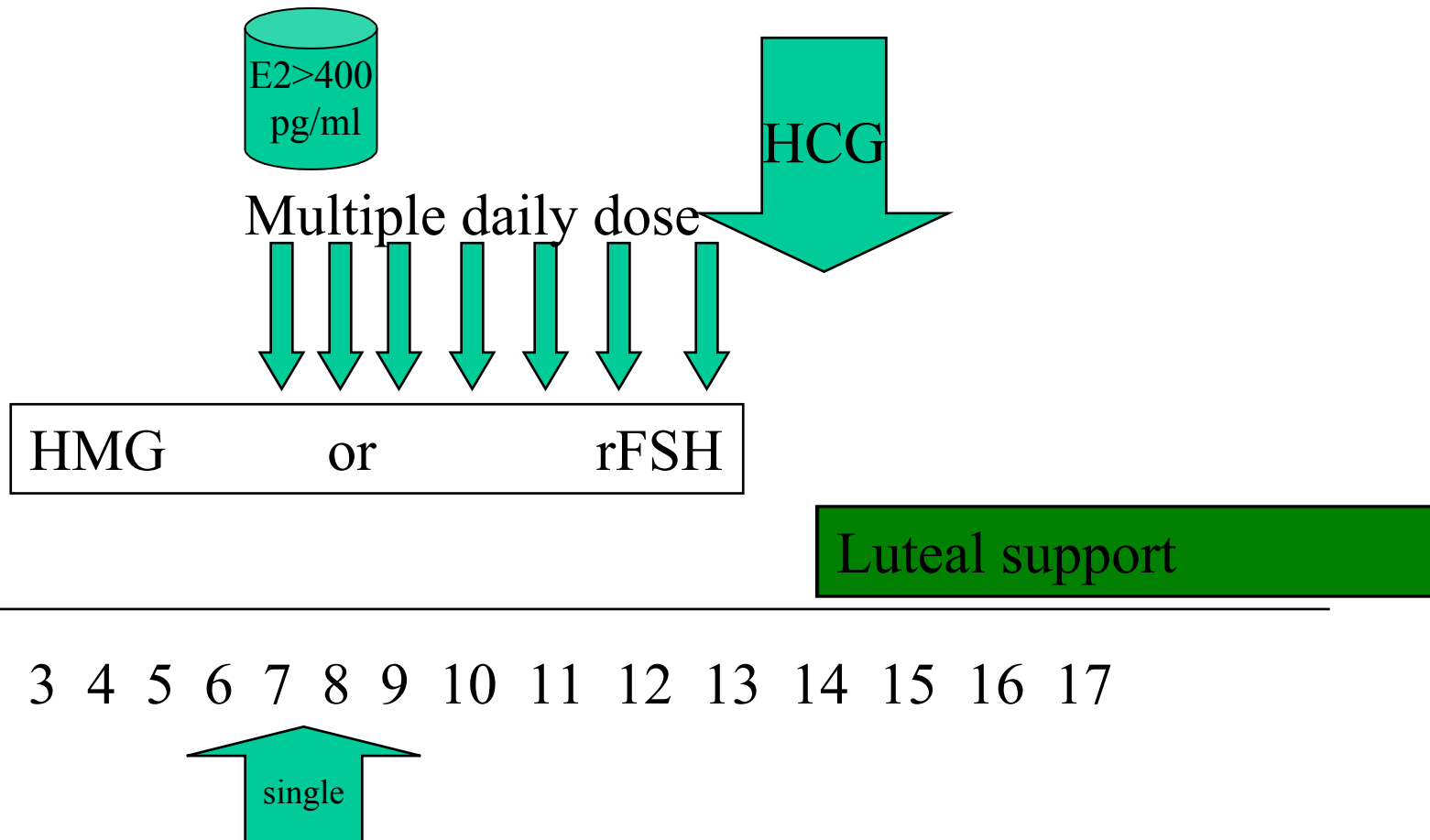
Plasma LH values in 2 mg and 3 mg cetorelix



Dosages in Assisted Reproduction

Single dose protocol : Cetrorelix

Multiple dose protocol : Cetrorelix or Ganirelix



Effect of GnRH Antagonists on Follicular Phase

- Stop follicular growth
- Normal follicular rescue
 - after terminal half life time of GnRH antagonist
 - with appropriate administration of gonadotrophins
- Transient decrease in E2 (related to dose)
- Decrease in total number of follicles
- No decrease in number of mature oocytes
- GnRH receptors found only after the LH surge

Effect of GnRH Antagonist on Luteal Phase

- Less impaired with antagonist than agonist
- still needs luteal phase supplementation
- P4 & E2 higher in cultured granulosa cells from women treated with antagonists > agonists
- Withholding luteal supplementation did not exclude pregnancy in some studies
- No impact on luteal phase when hormonal support is given

Multicentre trial of the European Orgalutran Study Group (ganirelix)

	Ganirelix	Buserlin
Median duration of analouge	5	26
Median total rFSH	1500 Iu	1800 IU
Incidenceof LH rise > 10 IU/L	2.8%	1.3%
Mean follicular number > 11 mm	10.7	11.8
Mean number of oocytes retrieval	9.1	10.4
Fertilization rate	62.1%	62.1%
On going pregnancy rate	20.3%	25.7%

Ovarian hyperstimulation syndrome (OHSS)

- WHO grade III **0.6%** (2/346)

Felberbaum et al. Hum Reprod 2000 May;15(5):1015-20

- WHO grade II-III GnRH antagonist(3.5%)

Agonist (11.1%)

Olivennes et al. Fertil Steril 2000 Feb;73(2):314-20.

- WHO grade III GnRH antagonist (**1.8%**)

Agonist (5.6%)

- Overall incidence GnRH antagonist (2.4%)

Agonist (5.9%)

Borm and Mannaerts. The European Orgalutran Study Group. Hum Reprod 2000 Jul;15(7):1490-8.

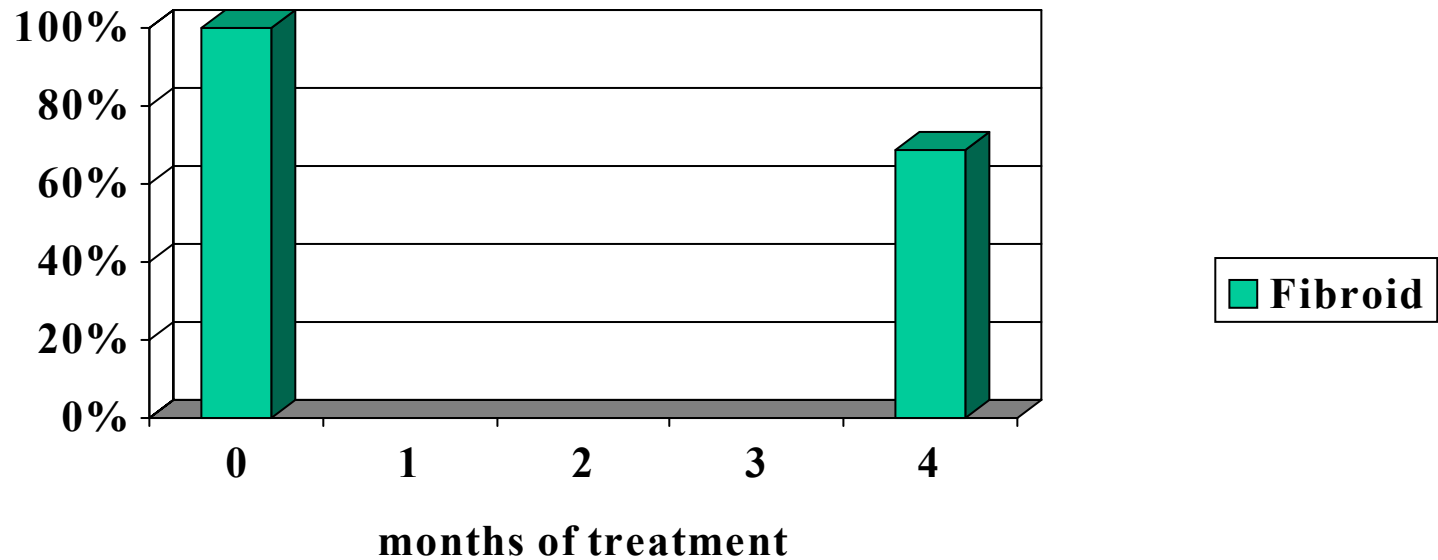
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- Lower incidence of OHSS
 - Less days of gonadotrophin stimulation
 - Lower number of ampoules
 - Mild headache on day of injection
 - Mild local injection reaction around 5%
 - No increased risk of miscarriage
 - No evidence of teratogenicity

GnRH antagonists in Gynaecological disorders

- Fibroids
- Endometriosis
- PCOD
- antitumour activity

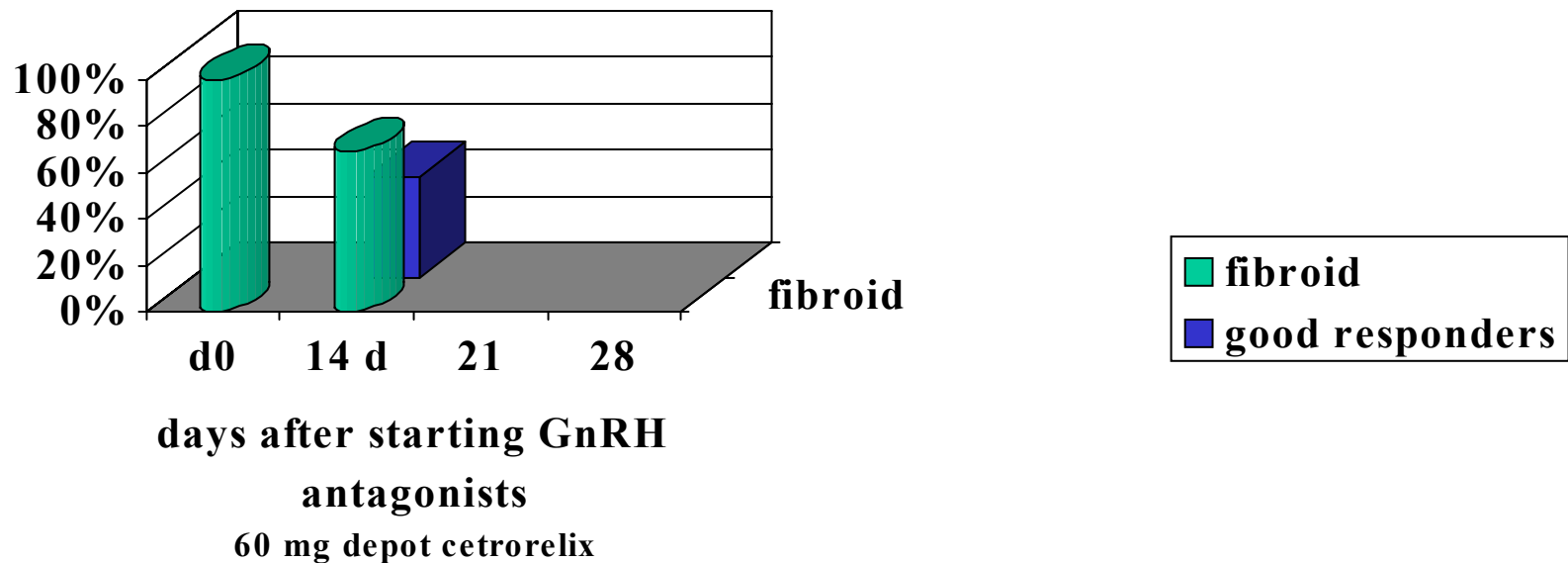
GnRH antagonist & Fibroids

5 mg b.d s.c for 2 dasys, then 0.8 mg daily s.c for 4.4 months



GnRH antagonist & Fibroids

Reduction in fibroid volume



GnRH Antagonists and tumour

- GnRH receptors (and GnRH antagonist effect) demonstrated in human malignant tumours, breast, ovary, endometrium and prostate
- inhibits the release of Insulin like growth factor and cell growth
- potential use in IVF, prior to chemotherapy in women wishing to become pregnant in the future.

Conclusion I

- Third generation GnRH antagonists have been evaluated in clinical studies
- Act by competitive blockage with GnRH
- Effective in immediate suppression of LH surge
- Avoid initial flare up effect
- Can be used in single or multiple dose protocols

Conclusion II

- Favourable outcome compared to agonists
- Low complication rate
- Well tolerated
- Reduce duration of treatment and total number of gonadotrophin stimulation and cost
- Rapid significant reduction in fibroid size
- Potential use in endometriosis and tumours
- GnRH antagonists may replace the agonist in gynaecology

Thank You