The Use of GnRH Antagonists in Gynaecology

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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)
    - Cetrorleix (Asta Medica)
    - Ganirelix (Organon)

Market approval

Hexapeptides, Heptapeptides
Decapeptide

1  2  3  4  5  6  7  8  9  10

Pyro-Glu  HIS  TRP  SER  TYR  GLY  LEU  ARG  PRO  GLY NH2

GnRH

Pyro-Glu  HIS  TRP  SER  TYR  LEU  ARG  PRO  NH2

GnRH Agonists

Ac-D-Nal(2)  D.Phe (4CI)  D/PA L  SER  TYR  D.hArg (Et2)  LEU  D.hArg (Et2)  PRO  D.AIA -NH2

GnRH Antagonists  Cetrorelix
**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)
Mode of Action: GnRH Agonists

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Mode of Action: GnRH Antagonists

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 cetrorelix

Dosages in Assisted Reproduction

Single dose protocol: Cetrorelix

Multiple dose protocol: Cetrorelix or Ganirelix

Multiple daily dose:
- E2 > 400 pg/ml
- HCG
- HMG or rFSH

Luteal support: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
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)

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<thead>
<tr>
<th></th>
<th>Ganirelix</th>
<th>Buserlin</th>
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<tbody>
<tr>
<td>Median duration of analouge</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Median total rFSH</td>
<td>1500 Iu</td>
<td>1800 IU</td>
</tr>
<tr>
<td>Incidence of LH rise &gt; 10 IU/L</td>
<td>2.8%</td>
<td>1.3%</td>
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<tr>
<td>Mean follicular number &gt; 11 mm</td>
<td>10.7</td>
<td>11.8</td>
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<tr>
<td>Mean number of oocytes retrieval</td>
<td>9.1</td>
<td>10.4</td>
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<tr>
<td>Fertilization rate</td>
<td>62.1%</td>
<td>62.1%</td>
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<tr>
<td>On going pregnancy rate</td>
<td>20.3%</td>
<td>25.7%</td>
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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%)
  GnRH Agonist (11.1%)
  

- WHO grade III GnRH antagonist (1.8%)
  GnRH Agonist (5.6%)

- Overall incidence GnRH antagonist (2.4%)
  GnRH Agonist (5.9%)

- 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

Gonzalez et al, 1997
GnRH antagonist & Fibroids

Reduction in fibroid volume

Felberbaum et al, 2000
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