Principles of Ovarian Stimulation
Oocyte development
Definitions

Ovulation induction
used where defect of ovulation
physiological event – one follicle, occ two

Superovulation
used in ART, sometimes with IUI (less because of multiple pregnancy)
stimulation of multiple fertilizable oocytes
not physiological
Clomiphene

• A selective oestrogen receptor modulator: anti-oestrogen – pituitary, breast, endometrium
• Given early in a menstrual cycle for five days
• Alteration of negative feedback leads to higher pituitary production of FSH and therefore (hopefully) ovulation
• Good for ovulatory disorders where some oestrogen e.g. PCOS
• Antioestrogenic effect on uterus/cervix : no place in IVF or frozen embryo transfer
Letrazole

- RCT suggests better than chlomiphene
- Not licenced in Australia for OI
Drugs using in superovulation

Gonadotrophins
- Recombinant FSH (Gonal F, Puregon)
- Recombinant LH (Luveris)
- Recombinant or urinary hCG (Ovidrel, Pregnyl)
- Urinary menotropins (Menopur)
FSH stimulation

Stimulation of a cohort of follicles to fertilisation capacity
Not physiological
Rapidly rising oestradiol ~ 1000 pmol/dl/follicle
Determined by ovarian reserve
Premature LH surge

Rapid/Large rise in oestradiol triggers release of LH from anterior pituitary: luteinization of follicles, ovulation

Premature release of LH needs to be suppressed
Drugs using in superovulation

GnRH analogues

- Agonists (nafarellin, leuprolide)
- Antagonists (ganirelix, cetrorelix)
Ongoing pregnancy rates (>12 weeks after ET)  
1000 cycle study (Out et al)

\[ p=0.01 \]

\[ p=NS \]

\[ p=0.02 \]

- Per started cycle
  - rec FSH: 22%
  - uFSH: 18%

- Per frozen ET
  - rec FSH: 16%
  - uFSH: 8%

- Per started cycle incl. frozen ET
  - rec FSH: 28%
  - uFSH: 20%

\[ n=585 \text{ rec FSH} \]
\[ n=396 \text{ uFSH} \]
\[ n=195 \text{ rec FSH} \]
\[ n=105 \text{ uFSH} \]
\[ n=585 \text{ rec FSH} \]
\[ n=396 \text{ uFSH} \]
LH / hCG?

- Do some patients respond better with the addition of LH or hCG?
- Potential benefit of rec LH in women over 35 years?
  - Marrs et al RBM Online Dec 2003
  - Humaidan et al RBM Online April 2004
Pituitary “switchoff”

GnRH agonists (Synarel, Lucrin)
- Initial stimulation of FSH and LH, then down regulation
- Best commenced about one week before FSH injections in luteal phase or whilst taking COC for greater than ten days

GnRH antagonists (Cetrotide, Orgalutran)
- Immediate effect
- Can be used when ovulation is at risk
GnRH agonists

• Initial flare up of gonadotrophins, then down regulation with prolonged use
• Internalisation of receptor-agonist complex, only partial recycling – decreased receptor number
• Post-receptor mechanisms
  ▪ Loss/impairment of receptor linked calcium channels
  ▪ Loss of transfer of gonadotrophin from a non-releasable to a releasable pool
• Down regulation persists after ceasing agonist
Long protocol

1. GnRH agonist
2. FSH
3. hCG

21 1

Prior luteal phase

Menses

11-14

Oocyte collection
Long protocol = gold standard

- COC
- GnRH agonist
- FSH
- hCG

Timeline:
- Menses
- Bleed
- Oocyte collection
Flare (short) protocol

GnRH agonist

FSH

hCG

Prior luteal phase
Menses
Oocyte collection
Meta-analysis comparing agonists

*Daya 1997*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Length</th>
<th>Favor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long vs short</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long follicular vs short</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long luteal vs short</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long vs ultrashort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long luteal vs long follicular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot vs daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours long or depot
Choice of protocol

• Long midluteal start significantly better in most studies
• No indication for short or flare protocol as first choice regimen
GnRH antagonists

- Direct inhibitory effect upon gonadotrophin secretion
- GnRH antagonists compete for and occupy pituitary GnRH receptors, preventing native GnRH occupation of receptor sites and therefore action
- Immediate action, but requires constant supply, delay in repeat dose is critical eg am am start
Antagonist protocol

GnRH antagonist

FSH

hCG

Prior luteal phase

Menses

Oocyte collection
Advantages of GnRH antagonists

- Shorter protocol
- Start antagonist at follicle size 12 mm or day 6 of FSH
- Lower incidence of OHSS
- Preferred by patients
Indications for GnRH antagonists

- Patient preference
- Poor responder
- Inappropriate responder?
- PCOS?
- Ovulation inhibition
  - Frozen ET
- Other “novel uses”
  - LH surge using GnRH agonist
**Meta-analysis comparing GnRH protocols of antagonists with agonists (I)**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Antagonist vs agonist</th>
<th>In favour of antagonist</th>
<th>Variable (95% CI; p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of analogue treatment per cycle</td>
<td>-19.48 days</td>
<td>✓</td>
<td>WMD (-21.05– -17.91)</td>
</tr>
<tr>
<td>Duration of FSH therapy</td>
<td>-1.13 days</td>
<td>✓</td>
<td>WMD (-1.83– -0.44)</td>
</tr>
<tr>
<td>OHSS less likely to occur</td>
<td>0.61</td>
<td>✓</td>
<td>RR (0.42–0.89; p=0.01)</td>
</tr>
<tr>
<td>OHSS-related hospitalisation</td>
<td>0.46</td>
<td>✓</td>
<td>OR (0.26–0.82; p=0.01)</td>
</tr>
<tr>
<td>Oocytes retrieved per cycle</td>
<td>-1.19 COCs</td>
<td>✓</td>
<td>WMD (-1.82– -0.56)</td>
</tr>
<tr>
<td>Embryos available for transfer</td>
<td>-0.74</td>
<td>✓</td>
<td>OR (-1.39– -0.08; p=0.03)</td>
</tr>
<tr>
<td>LH rise</td>
<td>8.27</td>
<td>✓</td>
<td>OR (3.82–17.90; p&lt;0.001)</td>
</tr>
<tr>
<td>LH surge</td>
<td>4.05</td>
<td>✓</td>
<td>OR (1.53–10.72; p=0.005)</td>
</tr>
</tbody>
</table>
Meta-analysis comparing GnRH protocols of antagonists with agonists (II)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of live birth</td>
<td>0.86</td>
<td>(0.72–1.02; p=ns)</td>
</tr>
<tr>
<td>Number of good quality embryos transferred</td>
<td>0.00</td>
<td>(-0.06–0.04; p=ns)</td>
</tr>
<tr>
<td>Incidence of multiple pregnancy</td>
<td>0.84</td>
<td>(0.59–1.19; p=ns)</td>
</tr>
<tr>
<td>Incidence of miscarriage</td>
<td>0.95</td>
<td>(0.61–1.49; p=ns)</td>
</tr>
<tr>
<td>FSH requirement (ampoules)</td>
<td>-3.04 ampoules</td>
<td>WMD (-6.27–0.19)</td>
</tr>
</tbody>
</table>

Adapted from Kolibianakis et al and Al-Inany et al. Primary and secondary outcomes reported in meta-analysis of clinical trials comparing GnRH antagonist with GnRH agonist protocols.

WMD=weighted mean difference; OR=odds ratio; RR=relative risk
Ovarian stimulation

• Low dose – leads to fresh transfer only (minimal stimulation push from Western Europe)

• High dose
  ▪ Cost impact to patient despite only modest (if any) increase in live birth per OPU
  ▪ Side effects of medications
  ▪ Social impact of injections
  ▪ Aneuploidy rate amongst embryos
IVF “Lite” – Macklon  *Lancet March 2007*

- 92 / 205 (45%) live births mild IVF
- 102 / 199 (51%) live births routine IVF
- Multiple pregnancy rates
  - 1% (mild) vs 13% (routine)
Mild ovarian stimulation

<table>
<thead>
<tr>
<th></th>
<th>150 IU / antagonist</th>
<th>225 IU / down regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome abnormal embryos (%)</td>
<td>45%</td>
<td>63%</td>
</tr>
<tr>
<td>FISH day 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Baart et al Human Reproduction Jan 2007*
The percentage of new patients who had their first egg pick-up in a two-year time period whose treatment resulted in a live birth after utilising their fresh or frozen embryos.

The percentage of these successful patients who had their child with three or fewer stimulated IVF cycles.
Can dropout be lessened by:

• Self injection systems?
• Lowering FSH dose? – side effects
• Newer stimulation techniques?
  ▪ Antagonist cycles
  ▪ Long acting agonists / antagonists
  ▪ Long acting FSH (Elonva)
Luteal support required?

• Long down regulation / use of agonists – YES
• GnRH antagonists – probably yes
• Other cycles?
Advantages of Progesterone

• Endogenous progestogen (cf progestin)
• Direct effect on endometrium
  ▪ First pass effect with vaginal approach
• Lower risk of OHSS

Progesterone pessaries (no pharmacokinetic data, no RCTs)
Crinone (RCTs, pharmacokinetic data)
Theoretical benefits of hCG

• Ease of use
• Long half life
• Encourages ovarian production of progesterone and oestrogen (and other factors?)

But – higher risk OHSS
Evidence

- No difference between hCG and progesterone
- Trend toward benefit from IM progesterone (dose issue)
- Benefit from additional estrogen?
Determining dose of FSH

Formal USS for PCO morphology
Age
AMH
Other factors: past experience, smoker
No evidence of increased oocyte retrieval over FSH 300 per day but increased aneuploidy in oocytes
GnRH agonist for trigger

Associated with significant reduction in OHSS

Associated with very poor pregnancy rate unless luteal support given

“Freeze all”
After oocyte collection

Corpora lutea need LH to maintain production of oestrogen and progesterone

If LH reduced: need luteal support
Drugs using in luteal support

Luteal support

- Progesterone (Crinone, progesterone pessaries)
- hCG (Pregnyl)
Summary – key points

• IVF and ICSI offer the best live birth rate for longstanding infertility
• Ovarian stimulation offers improved outcomes, but prevention of premature LH surge and release and luteal support are essential
• “Patient centred” IVF (ie lower FSH doses and less injections) now appear to not decrease pregnancy rates in IVF
Summary – key points

- Place of newer interventions such as GnRH agonist trigger, Elonva under development
- Reduced OHSS and multiple pregnancy is a national goal