Principles of Ovarian Stimulation

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Normal oocyte development
Types of Ovarian Stimulation

1. Ovulation induction
   - used for ovulation defects
   - mimic physiological event - 1-2 follicles

2. Superovulation (Hyperstimulation)
   - used in IVF/ICSI
   - stimulation of multiple fertilizable oocytes
   - not physiological
Ovulation Induction with Clomiphene Citrate

- 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 there is some oestrogen e.g. PCOS
- Antioestrogenic effect on uterus/cervix
Ovulation Induction with FSH

- When a woman fails to ovulate despite a maximum dose of clomiphene
- When a woman fails to conceive despite ovulating on clomiphene
- Not able to tolerate clomiphene

Principles:
- Low dose daily FSH injections
- Monitor E2 levels
- Confirm development of a dominant follicle with ultrasound
- Trigger ovulation
Other Drugs used in Ovulation Induction

- **Metformin**
  - Insulin sensitizer, Category C
  - Treatment of insulin resistance, androgen excess; may assist with LOW

- **Letrozole**
  - Aromatase inhibitor, Category D
  - Aromatase is an enzyme that catalyses the conversion of androgens to estrogens
  - OI without anti-E2 effects
Superovulation (Hyperstimulation)

- In IVF/ICSI cycles
- Aim is to produce multiple eggs, so higher doses of FSH required

Principles of Superovulation
1. FSH stimulation of multiple follicular growth
2. Suppression of premature ovulation with GnRH agonist or antagonist
3. Trigger ovulation
4. Luteal phase support
FSH stimulation

- Stimulation of a cohort of follicles to grow
- Not physiological
- Rapidly rising oestradiol
  - ~ 500-1000 pmol/dl/follicle
- Number of follicles that grow determined by
  1. Ovarian reserve
  2. Dose of FSH
Determining dose of FSH

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

- Recombinant FSH (Gonal F, Puregon)
- Urinary menotropins (Menopur)
- Long-acting FSH (Elonva)
- Biosimilars (Bemfola)
Prevention of premature LH surge

- Rapid/Large rise in oestradiol triggers release of LH from anterior pituitary: luteinization of follicles and ovulation
- Premature release of LH needs to be suppressed
Suppression of LH surge

- GnRH analogues
  - Agonists
    (nafarelin, triptorelin, leuprolide)
  - Antagonists (ganirelix, cetrorelix)
Pituitary “switchoff”

- GnRH agonists (Synarel, Decapeptyl, Lucrin)
  - Initial stimulation of FSH and LH, then down regulation
  - Best commenced either (i) one week before FSH injections in luteal phase, or (ii) whilst taking COCP 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 gondaotrophins, 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
Pill Down Regulation: long protocol

- GnRH agonist
- FSH
- hCG

Timeline:
- Menses
- Bleed
- Oocyte collection
Luteal Down Regulation

GnRH agonist

FSH

hCG

Prior luteal phase  Menses  Oocyte collection
Flare/Boost (short) protocol

GnRH agonist

FSH

hCG

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11-14

Prior luteal phase  Menses  Oocyte collection
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 start
Advantages of GnRH antagonists

- Shorter protocol
- Start antagonist at:
  - follicle size 12 mm = Flexible start
  - OR day 5 or 6 of FSH = Fixed start
- Lower incidence of OHSS
  - Option to use agonist as a trigger
- Preferred by patients - less side effects, no nasal spray
<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>
Antagonist protocol

Prior luteal phase | Menses | Oocyte collection

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GnRH antagonist

FSH

hCG
Meta-analysis comparing GnRH protocols of antagonists with agonists (II)

<table>
<thead>
<tr>
<th>No statistical difference (antagonist vs agonist)</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
Triggering Ovulation

- Ovulation needs to be triggered to ensure:
  - Final maturation of the eggs
  - Release of oocytes into follicular fluid
  - hCG is used to trigger ovulation and is given 36 ± 2 hours pre-egg retrieval
  - Recombinant hCG (Ovidrel)
  - Urinary hCG (Pregnyl)
GnRH agonist for trigger

- Associated with significant reduction in OHSS
- Can only be used in an antagonist cycle
- Associated with very poor fresh pregnancy rates due to reduction in luteal phase
- “Freeze all” protocol often applied
- Do not use if pituitary/hypothalamic disease
After oocyte collection - Luteal Phase Support

- Corpora lutea need LH to maintain production of oestrogen and progesterone

- Because GnRH analogues suppress LH production, may need luteal phase support
Luteal support required?

- Long down regulation / use of agonists - YES
- GnRH antagonists - probably yes
Drugs used in luteal support

- Luteal support
  - Progesterone
    - Crinone
    - Progesterone pessaries
    - Endometrin pessaries
    - IM progesterone
  - hCG (Pregnyl)
Progesterone

- Endogenous progestogen (cf progestin)
- Direct effect on endometrium
  - First pass effect with vaginal approach
- Lower risk of OHSS than hcg

IM Progesterone -
Trend toward benefit from IM progesterone (dose issue)
hCG

- Easy to use
- Long half life
- Encourages ovarian production of progesterone and oestrogen (and other factors?)

► BUT - higher risk OHSS
Goals with Ovarian stimulation

- Reduced OHSS
  - Lower doses of FSH
  - Antagonist cycle
  - Single embryo transfer
  - Agonist trigger and freeze all

- Reduced multiple pregnancy
  - Lower doses of FSH with ovulation induction
  - Single embryo transfer
Ovarian stimulation

- Low dose - may lead 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 and hyperstimulation
  - Possible increase in aneuploidy
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)