Principles of Ovarian Stimulation

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Learning objectives

• Ovarian physiology
• Types of ovarian stimulation
  • Oral agents and FSH
• Controlled ovarian hyperstimulation
  • Why and how?
• Risk reduction in IVF
Women are born with all the eggs they will ever have
Follicular development
AMH as marker of ovarian reserve
Types of Ovarian Stimulation

1. Ovulation induction
   - used for ovulation defects
   - natural conception, insemination
   - mimic physiological event – 1-2 follicles

2. Controlled ovarian stimulation
   - used in IVF/ICSI
   - stimulation of multiple oocytes
   - not physiological
• Aromatase inhibitor
• Originally used as decrease estrogen level for breast cancer
• In Australia – off label/ not licenced for OI
• Blocks formation of estrogen from androgen-> lowering circulating estrogen level
• Drop in estrogen level switches on estrogen production by the pituitary
• Encourage monofollicular development
• Given early in a menstrual cycle for five days
• Cochrane review favors letrozole over clomiphene
OI with Clomiphene Citrate

- SERM- selective estrogen receptor modulator
- structurally similar to estrogen -> binds to the estrogen receptor of the pituitary
- Convince pituitary cells that estrogen level is falling
- In PCOS, pituitary is intact- hence release FSH
- Process of ovulation begins
- Risk of multiple pregnancy

- anti-estrogen effect on ndometrium
OI with clomiphene/letrozole
Metformin

- Insulin sensitizer
- Treatment of insulin resistance, androgen excess; may assist with weight loss
- Evidence controversial
Indications
- Resistance to oral agents
- When a woman fails to conceive despite ovulating on letrozole/ clomiphene
- Side effects with oral agents, eg visual disturbance with clomid
- IUI

Principles
- Low dose daily FSH injections
- Confirm development of a dominant follicle with ultrasound
- Trigger ovulation

RISK – high multiple pregnancy (cancel if >2 follicles)
Controlled ovarian stimulation (COS)

Aim is to produce multiple follicles

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
If we collect **10** eggs for IVF

- **8** will be mature
- **6** will fertilise
- **4** will reach cleavage stage by day 2
- **1 or 2** will reach blastocyst by day 5
FSH stimulation

- Stimulation of a cohort of follicles to grow
- Rapidly rising estradiol ~ 500-1000 pmol/dl/follicle
- Number of follicles that grow determined by
  1. Ovarian reserve
  2. Dose of FSH
  3. Female Age
Determining dose of FSH

- Ovarian reserve – AMH/ AFC
- Age
- weight
- Previous stimulation cycles and response
- No evidence of increased oocyte retrieval over FSH 300 per day
FSH products

- Recombinant FSH (Gonal F, Puregon, Pergoveris, Rekovel)
- Urinary menotropins (Menopur)
- Long-acting FSH (Elonva)
- Biosimilars (Bemfola)
Do patients need LH as well as FSH?

- Required in women with hypothalamic amenorrhoea (ie. Low/no endogenous LH)
- Potential benefit of adding LH in women over 35 years or poor responders

Options
- Recombinant LH (Luveris)
- Combined Rec FSH and LH (Pergoveris)
Prevention of premature LH surge

• Rapid and large rise in estradiol 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 “switch off”

- **GnRH agonists** (Synarel, Decapeptyl, Lucrin)
  - Initial stimulation of FSH and LH, then down regulation
  - Best commenced in the luteal phase, one week before FSH injections

- **GnRH antagonists** (Cetrotide, Orgalutran)
  - Immediate effect
  - Can be used when ovulation is at risk
Long Down Regulation cycle

GnRH agonist

FSH

hCG

Prior luteal phase  Menses  Oocyte collection

21  1  11-14
Flare (short) protocol

1. GnRH agonist
2. FSH
3. hCG

- 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
Antagonist protocol

GnRH antagonist

FSH

hCG/ agonist trigger

21  1  11-14

Prior luteal phase  Menses  Oocyte collection
Advantages of GnRH antagonists

- Shorter protocol
- Start antagonist at:
  - follicle size 14 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 injections, shorter stimulation cycle, less hypoestrogenic side effect, nasal spray
Meta-analysis GnRH antag versus GnRH agonist protocols

Comparisons of GnRH antagonist protocol versus GnRH agonist long protocol in patients with normal ovarian reserve: A systematic review and meta-analysis

Conclusion
GnRH-ant protocol substantially decreased the incidence of OHSS without influencing the pregnancy rate and live birth rate compared to GnRH-a long protocol among patients with normal ovarian reserve.
Triggering Ovulation

- LH surge
- Resumption of meiosis
- Release of oocytes into follicular fluid
- Structural remodelling
- Luteinization to start progesterone production

- 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

- Virtually abolishes risk of OHSS
- Can only be used in an antagonist cycle
- Has reduced pregnancy rates if fresh transfer due to poor luteal phase
- “Freeze all” is almost routine
- Do not use if underlying pituitary/hypothalamic suppression (hypo hypo patients)
• Corpora lutea need LH to maintain production of estrogen and progesterone

• Options
  1. Use HCG (LH similar) - increased risk OHSS
  2. supplement with progesterone
Drugs used in luteal support

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

- Direct effect on endometrium
  - First pass effect with vaginal approach
- Lower risk of OHSS than hcg

IM Progesterone - Painful daily injection
hCG

• Easy to use
• Long half life (day 3, 6,9 after OPU)
• Encourages ovarian production of progesterone and estrogen
• BUT – higher risk OHSS
Risk reduction

- Reduce OHSS
  - Lower doses of FSH
  - Antagonist cycle
  - Agonist trigger
  - Freeze all, cancel fresh transfer
  - LPS with progesterone instead of HCG

- Reduced multiple pregnancy
  - Single embryo transfer
Thank you