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The management of ovulatory dysfunction

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Conflict of interest

none

Outline

- Causes of ovulatory dysfunction
- Assessment of women with ovulatory dysfunction
- Management
  - First line
  - Second line
  - Adjuvants
  - Co-morbidities

WHO Type I: Hypogonadotropic hypogonadism

Defects within hypothalamic-pituitary unit

- Isolated GnRH deficiency
- Hyperprolactinaemia
- Vascular (Sheehan's)
- Tumours
- Auto-immune
- Empty Sella

Abnormal CNS-hypothlalmic interaction

- Exercise-related
- Weight-loss related
- Psychogenic

Tests: FSH, LH, Oestradiol, Prolactin, MRI pituitary, genetic mutations

Features: Amenorrhoea, Low/normal LH/FSH with low Oestradiol

WHO Type II: Hypothalamo-pituitary dysfunction

- Most commonly Polycystic Ovary Syndrome
- Rotterdam criteria are commonly used but controversy persists
- Patient demonstrates two of three criteria:
  1. Oligo- or chronic anovulation
  2. Clinical and/or biochemical signs of hyperandrogenism
  3. Polycystic ovaries

  With Exclusion of other causes
- Should AMH be part of the diagnosis?
- Should a measure of insulin resistance be used?

Type III: Hypergonadotropic hypogonadism

- Ovarian failure
- Congenital - gonadal dysgenesis, Turner's Syndrome
- Acquired – chemotherapy, premature menopause
- Amenorrhoea, raised FSH
- Management is limited
  - Hormone Replacement Therapy
  - Donor eggs
  - In vitro activation is an experimental technique of interest (Kawamura et al 2017)

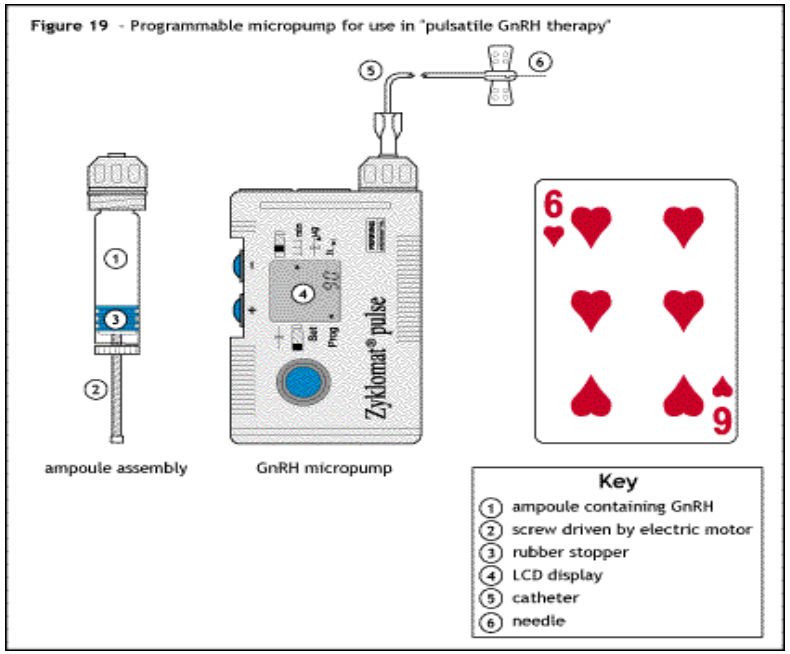
General principles of managing ovulatory dysfuntion

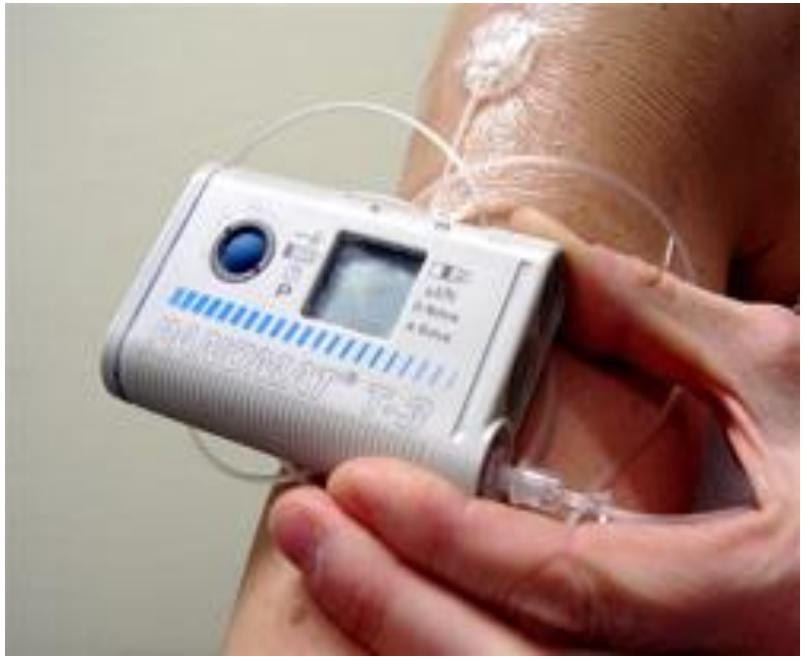
- Consider likely cause and type
- Consider overall fertility potential of the couple and co-morbidities
- Efficacy
  - Live birth rate per cycle started
- Safety
  - Ovarian Hyperstimulation Syndrome
  - Allergic reactions
  - Infection risk
- Cost and cost-effectiveness
  - Drug costs
  - Cancellation of cycle
  - Multiple pregnancy

Induction of ovulation in Type 1

- Weight optimisation – Specific psychotherapy
  - Focal psychodynamic therapy
  - Cognitive Behavioural Therapy
  - Slow and complex process
  - Return of menses may not occur despite weight gain
- Reduce Exercise
- Increase calorie intake
- Important to achieve a healthy BMI before starting fertility treatment

GnRH Pump



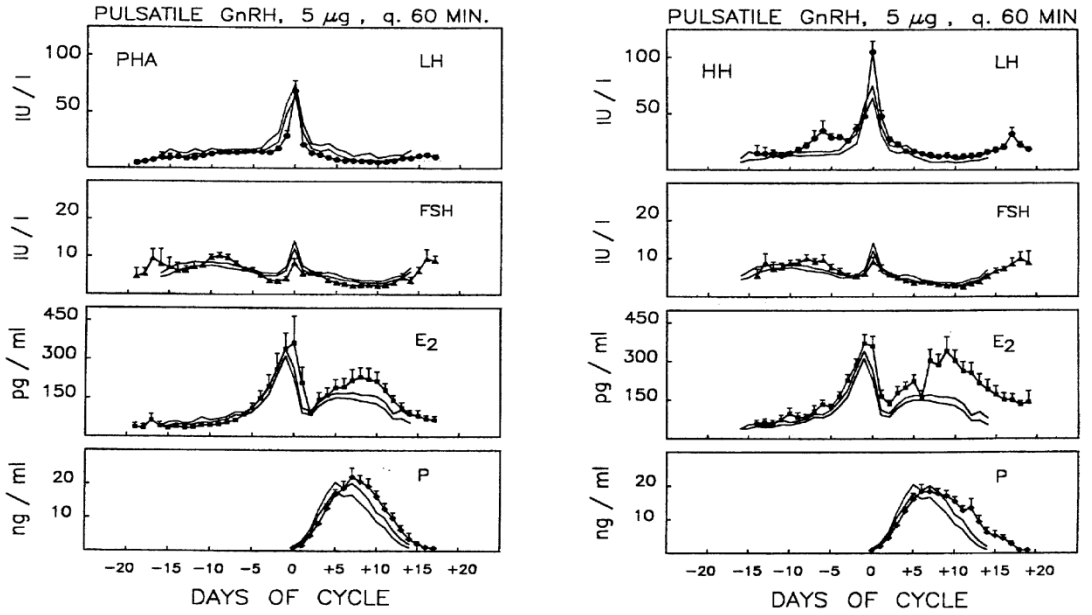


10 – 20 mcg sc or iv every 90 minutes

Results of GnRH pump in primary hypogonadotropic amenorrhoea

- Most patients have an intact pituitary, which responds to GnRH
- Ovulation occurs in 80 – 95% cycles
- Pregnancy in 30% cycles
- Over 12 months, conception rate is nearly 90% (similar to natural)
- Multiple pregnancy is rare
- Ovarian hyperstimulation is rare

GnRH pump response



- Pituitary remains sensitive to feedback, hence usually a single follicle develops, with E2 300-450 pg/ml
- Spontaneous LH surge and ovulation
- Normal luteal phase

Induction of ovulation in Type 1

- Recombinant Leptin (metreleptin)is effective in women with Hypothalamic Amenorrhoea (Chou et al 2011 PNAS), but poorly studied and not licensed for this.

- FSH/LH ovulation induction is more commonly used. May require prolonged treatment. There may be a benefit for Growth Hormone with panhypopituitarism.

Induction of ovulation in PCOS

- Weight management and lifestyle should be first line
- Difficult to maintain over long term
- Both dietary restriction and exercise should be advised, as exercise alone is usually not enough
- For instance, 30 minutes aerobic exercise 5 times a week plus reduction on calories by 500 kcal/day, aiming to lose 0.5 kg per week
- Very difficult to achieve and sustain, needs lots of support and input

Clomifene v Letrozole?

- Clomifene is an anti-oestrogen used since 1960
  - 50-150 mg daily from 2 or 3 for 5 days
- Letrozole is an aromatase inhibitor used since 2001 for ovulaiton induction
  - 2.5-7.5 mg daily from day 2 or 3 for 5 days
- Clomifene is most widely used, but Letrozole is likely to be as effective
- Cochrane review found increased live birth rate with Letrozole compared to clomifene for ovulation induction (OR 1.68, 95% CI 1.42 to 1.99; 2954 participants; 13 studies).
- Number needed to treat for an additional beneficial outcome (NNTB) = 10; moderate-quality evidence

Clomifene v Letrozole?

- No difference in risk of hyperstimulation or miscarriage
- However, practice has been slow to change
- Some doubts about quality of evidence remain
- It is not clear whether adding Metformin makes a difference
- Hence a UK randomised control trial is planned to start in 2019 comparing Letrozole to Clomifene, with and without metformin (2 x 2 factorial design) for ovulation induction in women with PCOS.

Options if first line treatment fails

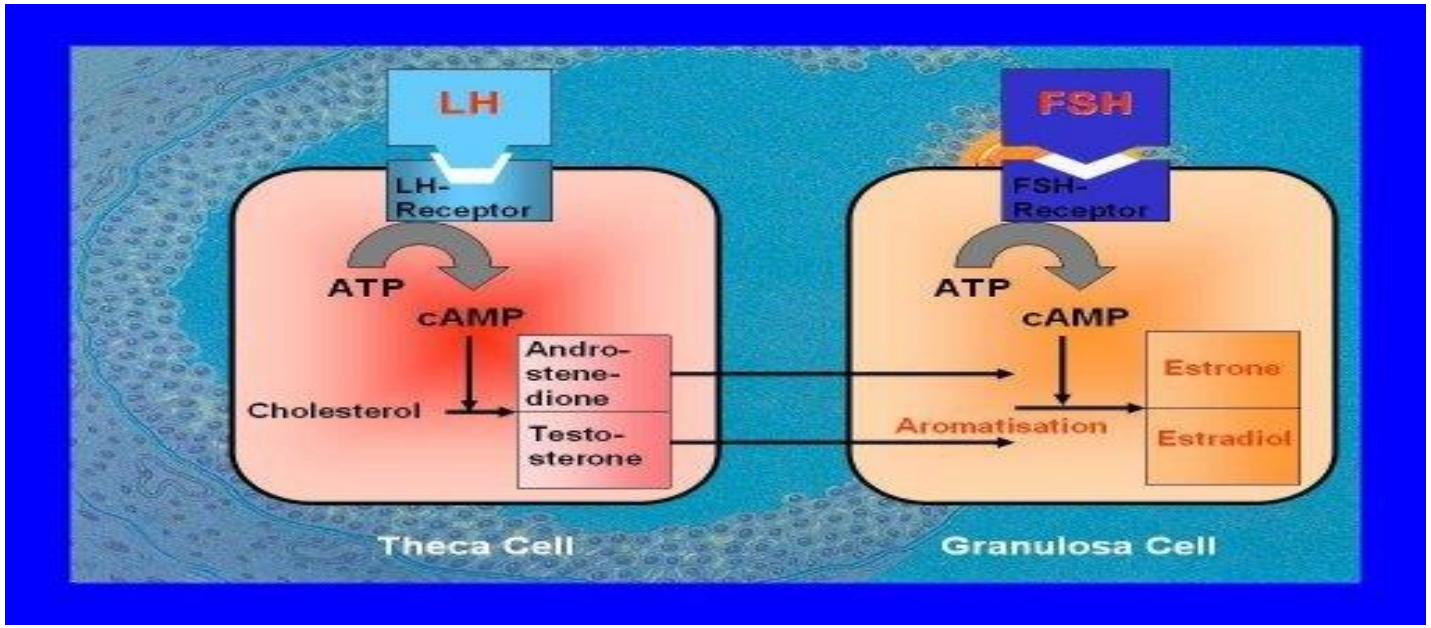
- Laparoscopic ovarian diathermy
  - Mechanism unknown – intra-ovarian androgen reduction, systemic lower E2
  - Leads to ovulation and live birth in 25 – 45% cases
  - Allows repeated pregnancy
  - No increased risk of multiple pregnancy
  - No risk of hyperstimulation
  - Cochrane review suggests it is equally effective as other methods
  - BUT – requires laparoscopy

Types of gonadotrophin

- **Urine-derived**
  - **Human Menopausal Gonadotrophin**: Standard ampoule has 75 iu FSH and 75 iu LH activity.
  - **Urinary FSH**: 75 iu FSH and 0.1 iu LH
  - **Purified urinary FSH**: 75 iu FSH and virtually no LH activity

- **Recombinant FSH**: from genetically engineered Chinese Hamster Ovary cells. Offers better purity, bio-availability and batch to batch consistency - but higher costs.
  - Follitropin α (Gonal F, Serono)
  - Follitropin β (Puregon, Organon)
  - Follitropin δ (Rekovelle, Ferring)
  - BIOSIMILARS

Role of LH in ovarian stimulation



In WHO Group I women, with very low LH and FSH levels, LH improves oestradiol secretion, FSH sensitivity and sensitivity to luteinisation by HCG

(ERhLH Study Group 1998, J Clin Endocrin Metabol 83; 1507-14)

However, in women undergoing pituitary down-regulation, the role of exogenous LH is not clear, even though their LH levels can be very low

Low LH levels are not associated with lower chance of ongoing pregnancy at IVF ***(Kolibianakis et al (2006) Hum Reprod Update 12, 3-12)***

Regimes for gonadotrophin OI

Low dose step-up regime

- Aims to slowly and carefully reach threshold for monofollicular development
- Start with rec FSH 50 iu for 14 days ('Chronic low-dose')
- Increase by 25 iu after ≥14 days if no follicular response
- Further careful increases after ≥7 days

Step-down regime

- Start with higher FSH dose (rec FSH 100 iu)
- Reduce dose after follicular response (>9 mm) to 75 iu, then 50 iu

Monitoring

- Transvaginal ultrasound
- Serum Oestradiol concentration

Table II. Clinical results of step-up and step-down administration of recombinant human FSH

	Step-up protocol (n = 85 cycles)	Step-down protocol (n = 72 cycles)	P
Duration of treatment (days)	15.2 ± 7	9.7 ± 3.1	< 0.001
Total amount of rFSH (IU)	951 ± 586	967 ± 458	NS
Rate of monofollicular development (%)	68.2	32	< 0.0001
Rate of bifollicular development (%)	15.3	23.6	NS
Rate of multifollicular (>3) development (%)	4.7	36	< 0.0001
Estradiol plasma value at hCG (pg/ml)	454 ± 465	849 ± 1115	< 0.05
hCG administration (%)	84.6	61.8	0.001
Rate of hyperstimulation (%)	2.25	11	0.001
No response (%)	11.8	8.33	NS
Progesterone > 8ng/ml (%) in luteal phase	70.3	61.7	0.02
Pregnancy/cycle (%)	18.7	15.8	NS

Step-up regime associated with greater incidence of mono-follicular ovulation, lower over-response and lower cancellation rates than **step-down** regime

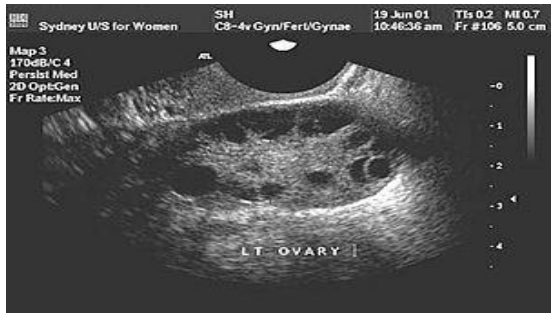
(Christin Maitre et al 2003 Hum Reprod 18; 1626-31)

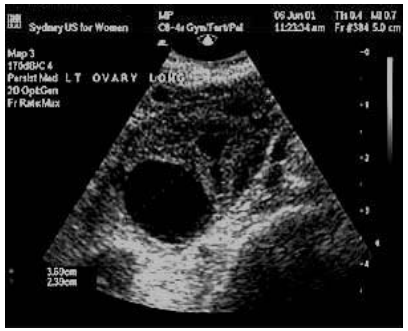
Results of gonadotrophin Ovulation Induction

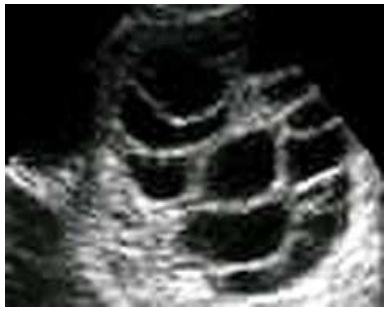
- Ovulation in 80 – 90% cycles
- Pregnancy rates 10 -15% per cycle
- Cumulative pregnancy rates 60% in 6 cycles
- Multiple pregnancy rate should be in single figures

Risks of gonadotrophin Ovulation Induction

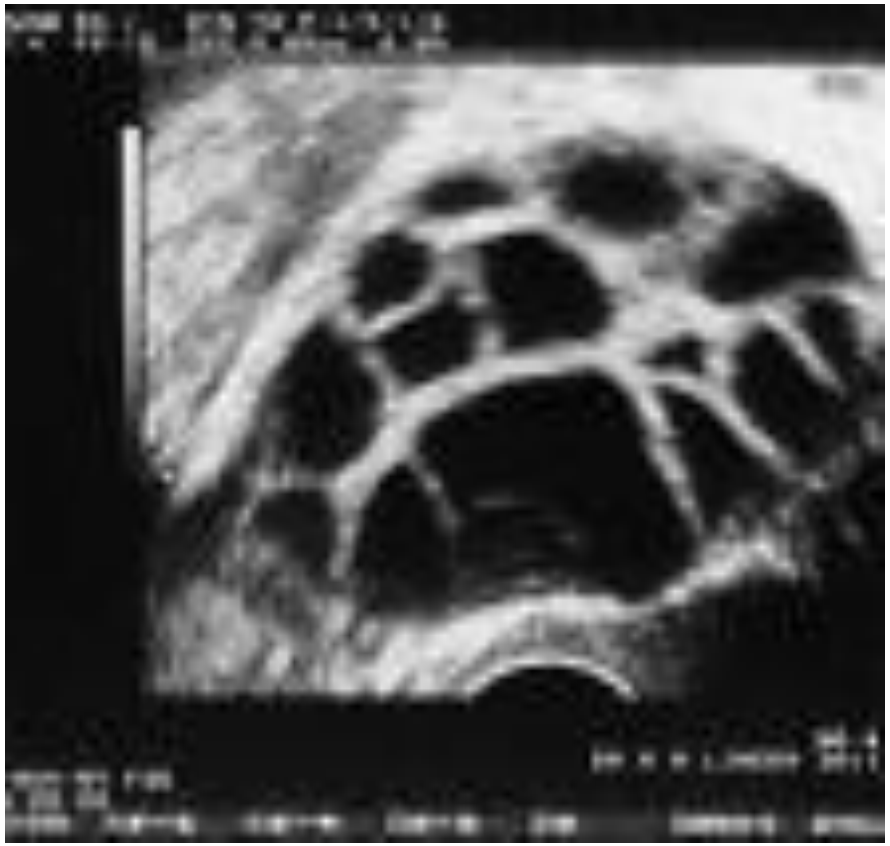
- OHSS and multiple pregnancy
- Large cohort of FSH-sensitive follicles
- Narrow range between threshold for mono-follicular development and threshold for multi-follicular development
- Role for metformin in reducing hyperstimulation







Ovarian hyperstimulation (OHSS)



- **Young age**
- **Low body weight**
- **Polycystic ovary syndrome (PCOS)**
- **Higher doses of gonadotropin injections**
- **High or rapidly rising levels of estrogen hormone through the stimulation phase**
- **Previous episodes of OHSS**

Dopamine agonists -Cabergoline and Bromocriptine

- Inhibit pituitary prolactin secretion, allowing normalisation of GnRH secretion
- Bromocriptine usually 2.5 mg bd, Cabergoline usually 1mg weekly
- Nausea, headaches, orthostatic hypotension, neuropsychiatric disturbances (LSD-related), retroperitoneal fibrosis, excessive, sudden sleepiness

Dopamine agonists

- About 80% patients re-start periods within 6 weeks of starting treatment
- Pregnancy rates similar
- Galactorrhoea may take much longer to resolve (50% at 12 weeks)
- Stop treatment if patient conceives
- Very small risk of serious enlargement of pituitary adenoma in pregnancy

Pregnancy following Dopamine agonists

- Microadenomas may enlarge in around 2% cases, macro- in slightly more
- Enlargement responds to Dopamine agonists
- No specific monitoring during pregnancy, other than awareness of symptoms (headache, visual defects)
- Microadenomas often regress following pregnancy (?infarction)
- Macroadenomas usually return on stopping treatment

Take-home messages

- Identify the type of ovulatory dysfunction
- The commonest condition in practice is PCOS
- Management depends on cause, but also on other co-existing problems and fertility factors
- GnRH pump is a good option for hypothalamic failure patients
- Lifestyle modification should always be considered in obese PCOS
- Letrozole is likely to be as effective as Clomifene in PCOS
- Laparoscopic ovarian diathermy is probably as effective as FSH ovulation induction in PCOS

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