Conventional ovarian stimulation no longer exists: welcome to the age of individualized ovarian stimulation

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Introduction

- Long gonadotrophin releasing hormone agonist protocol with maximal-dose gonadotrophins
- Mainstay of ovarian stimulation in IVF for decades
- Efficient patient timetabling
- Low cancellation rates
- High numbers of pre-ovulatory follicles, oocytes and embryos → improved pregnancy rates

  (Hugues et al., 1992)
- Time-consuming, expensive, not patient friendly

  (Ubaldi et al., 2007)

GnRH antagonist regimens

- ↓ Treatment times
- ↓ Total gonadotrophin doses and costs
- ↓ Risks of ovarian hyperstimulation syndrome (OHSS), (Devroey et al., 2009)
- *'One size fits all' from simplistic approach*

Identifying patients benefit from which form of LH suppression

- 1º end-points:
- Degree of ovarian response → Marker of safety, implantation & pregnancy outcomes
- Variety of options (agonist vs. antagonist) protocols based upon anticipated ovarian response → more likely to attain optimal outcomes for patients and physicians → More standardized approach to ovarian stimulation
- Manchester, UK in November 2009

The downside of one size fits all: which approach is optimal?

- GnRH antagonists ⇔ agonists
- *Initial trials:*
  - Unsatisfactory
  - No superiority in pregnancy outcomes

    (Albano et al., 2000; Borm and Mannaerts, 2000)

Meta-analyses

(Al-Inany et al., 2006):

- Marginally ↓ pregnancy/ ongoing/live-birth rates
- Non-peer-reviewed data/studies of IUI

(Kolibianakis et al., 2006):

- Different outcome in live birth rates
- Excluded Non-peer-reviewed data/studies of IUI
- Estimated some live births from ongoing pregnancies: 84% viable at 7 weeks or 92% viable at 12 weeks
- Easily altered with further moderate-sized trials

- Restriction of meta-analyses to special patient groups (poor responders & those with PCOS)

→ failed to demonstrate significant benefits with respect to clinical pregnancy *(Griesinger et al., 2006)*

- A trend towards ↓ success with antagonists ⇔ ↓ of OHSS risk *(Al-Inany et al., 2006; Griesinger et al., 2006)*

Lack of evidence

Optimal protocols have yet to be established *(Devroey et al., 2009; Huirne et al., 2007; Macklon et al., 2006)*

- Optimal starting dose
- Dose adjustments
- Day of start of GnRH antagonist
- Criteria, timing, mechanism for oocyte maturation
- Timing of the commencement of stimulation by FSH alone ⇔ alternatively human menopausal gonadotrophin (HMG) ← relatively small studies

Criteria for treatment

- > 20 different antagonist protocols → Recent a 'best estimate' protocol for use in predicted normal responders (Devroey et al., 2009) → Restrictive
  - < 35 y/o
  - 5–9 follicles / ovary
  - no history of PCOS, endometriosis or previous poor response
- Age criterion (Within European) → exclude50% patients embarking on IVF, 45.3% ICSI (Nyboe Andersen et al., 2009)

Summary of available conventional protocols for ovarian stimulation	
Protocol	Agent
Long, short and microflare	GnRH agonists and r-FSH, HMG, r-FSH plus r-LH and other adjunctive agents
Standard, mild and modified natural cycle	GnRH antagonists and FSH, HMG, FSH plus LH and other agents such as clomiphene citrate
Minimal and natural cycle	No GnRH analogues and FSH, HMG and FSH plus LH

Alternatives to one size fits all

- Conventional ovarian stimulation for all patients no longer exists

- Additional modifications in ovarian stimulation

→*improve response in women* → *suboptimal response to 'conventional' protocols*

→altered timing and dose of agonist administration

→Various combinations of gonadotrophins

  →in particular the addition of LH

  →pretreatment with testosterone, dehydroepiandrosterone (DHEA), human chorionic gonadotrophin (HCG), oestrogen, growth hormone and letrozole

Poor response

- Lack of uniform definition of 'poor response'
- Conventional Tx in the 1st stimulation cycle
- [Oestradiol]: < 800–900 pg/ml
- Small number (3, 4 or 5) of mature follicles

➔ Conventional approach: ↑ Gonadotrophin dose

High doses of gonadotrophins

- >300 IU FSH/day → in an individual *with a limited number of antral follicles* → likely to have no impact upon response/all FSH-sensitive follicles will be recruited by normal or excessive doses
- Oocyte quality: no evidence of enhanced → difficult to explaining how the additional exogenous gonadotrophins may be beneficial
- In high-responder donors → ↓ FSH dose → may improve fertilization rates and embryo quality

→Individualized using the 'minimal effective dose' in each patient and donor for optimal IVF outcome

The role of LH

- There is no consensus on the threshold concentration of endogenous LH required for optimal ovarian stimulation
- During ovarian stimulation → Minimum LH threshold value with FSH alone → ineffective (Cabrera et al., 200)
- Other studies: GnRH agonist/IVF → low serum concentrations of LH (Balasch et al., 2001) ⇔ GnRH antagonist → conflicting LH concentrations in cycles (Kolibianakis et al., 2003, 2004)

LH activity

- From HMG preparations, HCG, r-LH, r-HCG
- Pregnancy/live-birth rates: HMG ⇔ r-FSH

→Most meta-analyses: non-significant differences

→Higher rate in others studies

→The most comprehensive meta-analysis

  - 16 studies, 4040 patients → **fewer oocytes** (1.54, 95% CI 2.53~0.56, P < 0.0001)
  - Need ↑total dose (mean difference 235.46 IU/l, 95% CI 16.62 ~ 454.30, P=0.03; standardized mean difference 0.33, 95%CI 0.08~0.58, P= 0.01)

- Molecule of LH to accounted for the entire LH activity in the original HMG preparations
  - → HCG (more available, partially purified urinary formulations)
  - HMG ⇔ r-FSH → milder stimulation response → higher cancellation rate due to poor response

- The effect of r-LH administration has to be seen in the context of selected groups of patients.
- The Nordic LH Study in unselected patients randomized on stimulation day 1 to either r-FSH with or without supplementary r-LH in a GnRH agonist protocol → no differences in ongoing pregnancy rates (Nyboe Andersen et al., 2008).

- One randomized trial: significant differences according to patient age groups (Marrs et al., 2004).
- Implantation rates:
- < 35 years, FSH alone > r-FSH + LH (30.7 ⇔ 23.5%)
- > 35 years, LH > FSH alone (21.7 ⇔ 15.7%)

➔ aged women (>35) ➔ derive a benefit from supplementary LH activity

- *Similar results were found in a further randomized study when normo-gonadotrophic women (*LH supplementation starting from day 8 of the cycle*)*
- no overall difference in pregnancy rates
- significantly higher implantation rates (36.4 ⇔ 13.3%) and reduced total FSH consumption
- r-LH supplementation (150 IU daily) was more effective than ↑ the dose of exogenous FSH in women with an initial suboptimal response *(De Placido et al.)*

HCG

- Supplement to FSH in the late follicular phase
- In long and short agonist and antagonist protocols recent meta-analysis of nine studies *(Kosmas et al., 2009)*

→HCG supplement in the GnRH antagonist group

→nonsignificant benefit in clinical pregnancy rate (odds ratio 1.54, 95% CI 0.98–2.42).

- A pilot study (2009): compared the effect of HCG supplementation/in GnRH antagonist cycles → ↓ in FSH consumption, comparable rates of oocyte yield and pregnancy in the HCG/control groups

- There is no evidence that supplementation with LH activity is necessary in an unselected IVF population,
- It may yet be beneficial in subgroups of patients: older women (usually need high doses of FSH)

Androgen supplementation

- Follicular survival (before they become sensitive to gonadotrophins)
- Promote granulosa cell functions in antral follicles

➔A means to both ↑ follicle numbers and improve their paracrine function

- Androgens ⇔ folliculogenesis lies in the model of PCOS → excessive granulosa cell activity, abnormal follicular development and hyperandrogenaemia
- Androgens enhance the mitogenic effect of oocytes and the growth factor GDF9 → these mechanisms are also present in PCOS

- The decline in both androgen and anti-Mu¨llerian hormone (AMH) concentrations was only modest in two studies with metformin (Fleming et al., 2005; Piltonen et al., 2005), and when dexamethasone was added in a third study, there was no effect on AMH, despite a fall in androgen concentrations (Carlsen et al., 2009)
- Protracted androgen treatment will improve poor ovarian reserve

- Induced hyperandrogenism → ↑ ovarian oxidative stress → enhanced ovarian prostaglandin E production, increased number of T lymphocytes and decreased expression of the long isoform of the leptin receptor → impair early follicle development

benefit from androgen supplementation

- Some small studies: supplementation over 17 weeks with the weak androgen DHEA → improved response to ovarian stimulation → significantly higher oocyte yield, number of oocytes fertilized, average embryo scores /oocyte
- A study: in women with diminished ovarian reserve(determined by circulating [AMH]) → after a minimum of 1 month's treatment with DHEA (25 mg orally, 3 times/day) → significant increase in AMH (Goyal et al., 2009).

- Those with an increase in AMH during treatment → had a higher chance of pregnancy.
- 33 women with reduced ovarian reserve → significantly higher live-birth rate in the DHEA group(75 mg daily)
- The positive effect of DHEA in selected women with diminished ovarian reserve:
  - May be related to stimulation of steroidogenesis and/or orchestration of growth factors
  - Insulin-like growth factor (IGF)-I in the ovary

- Shorter-term concept: paracrine functions of antral follicles growing under the influence of gonadotrophins.
- Between granulosa & theca cells: A constant dialogue exchanged (steroidogenesis & growth) + androgens derived from theca cells → promoting granulosa cell sensitivity to FSH
- therapeutic approaches → improved function rather than increased follicular numbers, because the number of antral follicles present at this stage has already been determined by preceding events

- One study: 25x patients, 2 previous cycle cancellations due to poor follicular response, normal basal FSH → Pretreatment with transdermal testosterone (20 g/kg per day) → 80% patients reaching oocyte recovery and achieving a clinical pregnancy rate of 30% per oocyte retrieval
- Another randomized study: short-term transdermal testosterone (2.5 mg/day) → little encouragement for a beneficial effect on follicles, metaphase II-retrieved oocytes or high-quality embryos

- Recent controlled study: Pretreatment with transdermal testosterone in patients with normal baseline FSH → improves the ovarian sensitivity to FSH → ↓ incidence of low response;↑ number of women reaching egg collection
- A prospective randomized double-blind placebo-controlled crossover study: effect of exogenous testosterone pretreatment in women aged between 38–45 years on ovarian folliculogenesis and steroidogenesis → ↑ testosterone concentrations, no effect on follicles >10 mm

- Peripheral androgens have little or no direct impact at the follicular level, (local concentrations are some > 1000x the peripheral circulation
- Any effect from short-term administration, is likely to be by a more indirect mechanism
  - LH or HCG administration → promote theca-cell activity
  - Aromatase inhibitors → increase intra-follicular androgen concentrations before FSH mediated recruitment.

LH pretreatment *Durnerin et al., 2008*

- Down-regulated IVF patients randomized to either
  - 1 week's pretreatment with r-LH
- continuing down-regulation prior to ovarian stimulation without pretreatment
- No indication of any quantitative effect(follicular sensitivity to FSH or ovarian hormone secretions) → oocyte yield: non-significant ↑, normal embryo yield (5.1 ~ 7.0 per patient): significant ↑
- ↑ LH activity in the treatment group → ↑ small antral follicle count at the start of FSH treatment

aromatase inhibitor *(Lossl et al., 2008)*

- Letrozole + HCG before ovarian stimulation as androgen priming
  - Higher Proportion of antral follicles developing to 14 mm
  - ↑ follicular fluid androgen concentrations was confirmed after egg collection.
- Failed to demonstrate significant differences in the number of oocytes retrieved and the number of top-quality embryos.

Growth hormone supplementation

- Growth hormone → up-regulating the intra-ovarian synthesis of IGF-I → augmentation of aromatase activity, oestrogen production, stimulation of follicular development and oocyte maturation → modulates the effect of exogenous gonadotrophins on granulosa cells

- A recent Cochrane meta-analysis of RCTs:
  - GH used routinely in IVF → no difference in outcome measures and adverse events → statistically significant difference in live-birth rates → the use of GH in known poor responders not increasing the adverse events
  - Limitations: few trials included, small sample size, diverse definitions of poor response used by the different authors

Patient selection

- Patient's goal from ART: a healthy live birth
- Respond differently to ovarian stimulation

→ Optimization of response and outcomes whilst minimizing the risks.

- Conventional outcome determined: number of oocytes retrieved in a Tx cycle → inappropriate with legal constraints on the number of oocytes available for fertilization or indeed on embryo freezing, and also when an excessive response puts the patient's wellbeing at risk.

Predictive value of ovarian response tests

- Chronological age, basal serum FSH concentrations, body mass index and the number of antral follicles may all affect and predict outcome (Howles et al., 2006; Klinkert et al., 2005b).

→ modelled into an algorithm → determine individual FSH starting dose as a reflection of ovarian response *(Olivennes et al., 2009)*

- A median of 9.0 oocytes were retrieved from the 5 possible dose groups (75–225 IU), all within an expected range of 'normal response'

(Olivennes et al., 2009)

- Only 2 patients (out of 161) → severe OHSS, 14.3% of cycles were cancelled for inadequate response.
- High cancellation rate (similar to that reported in a randomized trial of mild IVF) *(Heijnen et al., 2007)*

→Individualized ovarian stimulation through simply modifying the FSH dose

→Other components: source of FSH, LH blockade strategy

Predictive value of ovarian response tests

- Basal FSH, inhibin B, oestradiol, ovarian volume and vascular flow, antral follicle count and AMH

- AMH: can be measured on a random plasma sample at any point in the menstrual cycle and is highly reproducible (van Disseldorp et al., 2010)
- Detailed studies looking at normative data for inter- and intra-cycle variability in different ethnic populations remain to be performed.

AMH

- Especially correlated with ovarian response
- Plasma concentrations ⇔ women at risk of extremes of response (La Marca et al., 2010).
- High AMH ⇔ Significantly with oocyte yield, good-quality embryos and live birth (Majumder et al., 2010; Nelson et al., 2007)
- Better predictor of live birth and oocyte yield than chronological age and FSH → better help determine the individualization of dose & strategy prior to ovarian stimulation (Nelson et al., 2007)

AMH concentration

- 1–5 pmol/l: at risk of either cycle cancellation or poor response
- 5-15 pmol/l: high probability of a normal and safe response to a standard long course down-regulation strategy
- >15 pmol/l: at risk of excessive responses thus requiring a protocol mindful of OHSS risk – that is with antagonist control and modest FSH doses
- >25 pmol/l: The risk of OHSS is substantial

- **AMH ⇔ oocyte yield** > chronological age, ovarian volume, FSH, oestradiol, inhibin B concentrations on day 3
- AMH prior to entering the first cycle of ovarian stimulation → ovarian performance assessment

→may be useful approach to individualize treatment

→optimize the chance of live birth

→allow the clinician to adapt a stimulation strategy (aim: minimizing risks at the extremes of response) *(Nelson et al., 2009)*

Conclusions

- The ability of women to respond to ovarian stimulation regimens is highly variable and although it declines with age, age alone is a poor indicator

- The **prediction** of extremes of response and the irreversibility of ↓ ovarian reserve have been one of the most debated issues of IVF treatment in the last decade.

- Entering ovarian stimulation without knowledge of individual ovarian potential is *unacceptable* owing to the ethical, psychological, financial and health consequences of extremes of response.

- Nevertheless, there are differences in the practical approach to stimulation depending on the country, demographics, funding stream and existing guidelines.

- Individualizing ovarian stimulation (Modifying conventional stimulation protocols according to patients' characteristics)

- Standard patient-friendly stimulation protocols with low doses of gonadotrophins

Excessive ovarian response

- Associate a high risk of OHSS & cycle cancellation

➔Can be reduced significantly

➔By ovarian stimulation treatment with low-dose gonadotrophins and GnRH antagonists,

low ovarian reserve & poor ovarian response

- ➔Management remains controversial.
- ➔Simply increasing the dose of gonadotrophins may not be optimal to stimulate the development of the follicle cohort which has ***already entered the process of recruitment by this time.***
- Therefore, priming ovarian function prior to commencing ovarian stimulation may prove to be a sensible approach, although the available data need to be confirmed and, as such, patients should be made aware of the still limited evidence.

- Some exogenous agents – LH, HCG, testosterone, DHEA and aromatase inhibitors

✓ Contribute to the paracrine regulation of the early stages of follicular maturation and atresia

✓ May play a role in controlling ovarian response in women with suboptimal ovarian performance

LH administration

- In older women as well as in those with evidence of compromised ovarian performance irrespective of chronological age, may improve cycle outcomes

Androgens

- May also have a beneficial role in selected patient types (⇔*FSH affect the predevelopment stages of the follicle's cycle*)

- Current necessaty
- Research androgen-mediated follicular dynamics
- Determining the daily dose, time and duration of androgen supplementation → folliculogenesis and individualize treatment

Thank you for listening