Milder is better? Advantages and disadvantages of "mild" ovarian stimulation for human in vitro fertilization

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Background

IVF / natural, single-egg cycle: very limited effectiveness

=> medications to induce multiple ovulation

↑ the number of oocytes available for fertilization

The potency of medicine to get more oocytes

•ovarian stimulation → low number of developing follicles → Cancelling cycle

•More oocytes-more embryos-more pregnancies = better IVF program

•live birth rate/inseminated oocyte: ~2-4%.

Recruitment, selection and dominance of follicles in ovarian physiology

- Complete follicular development

➢ ~ 220 days

➢ 3 distinct phases (According to developmental stage/pituitary gonadotropins):

(a) Initial recruitment of resting primordial follicles

(b) Development of preantral and early antral follicles

(c) Cyclic recruitment of a limited cohort of antral follicles ➔ the selection of a single dominant follicle

Recruitment, selection and dominance of follicles in ovarian physiology

- Complete follicular development
  - ~ 220 days
  - 3 distinct phases (According to developmental stage/pituitary gonadotropins):

Regulated by
Intra-ovarian factors/
Gonadotropins

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(b) Development of preantral and early antral follicles

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Recruitment, selection and dominance of follicles in ovarian physiology

- Complete follicular development
  - ~ 220 days
  - 3 distinct phases (According to developmental stage/pituitary gonadotropins):

Begins during the luteal-follicular transition (FSH ↑ → > a cohort of small antral follicles is recruited to grow)

(a) Initial recruitment of resting primordial follicles

(b) Development of preantral and early antral follicles

(c) Cyclic recruitment of a limited cohort of antral follicles → the selection of a single dominant follicle

- *Begin of **follicular growth*** (morphological change)
  - Granulosa cells (proliferation, change in shape)
  - Oocyte (enlargement, zona pellucida formation)
- *End of the primary follicle stage*: early theca acquired ➔ external theca → follicle grows and compresses the surrounding stroma

- Early preantral follicle development
- (FSH, estrogen and androgen) receptors appear on the granulosa cell surface
- Follicle unaffected by the lack of gonadotropins
- FSH blood levels → Initial rise → **Plateau** during the early follicular phase and finally **decrease** during the mid-to-late follicular phase (as a consequence of the *negative feedback* exerted by *inhibin B* and *estrogens* on the hypothalamic-pituitary axis)

- *The presence of FSH is an absolute requirement for the development of larger antral follicles*
- Around the mid-follicular phase, the most mature follicle (the one with the highest number of FSH receptors on granulosa cells) gains **dominance** over the others
- despite progressively ↓ FSH blood levels, the dominant follicle continues to grow and acquires responsiveness to LH. (remaining follicles → atresia)

basis of the "mild" stimulation strategy

- Moderate but continued elevation of FSH during the mid-to-late follicular phase
  - →extend the FSH window
  - →overcome the single dominant follicle selection
  - →leading to the growth of several follicles
- In the "mild" ovarian stimulation, a low-dose gonadotropin administration is delayed until the midfollicular phase (day 2-to-5 of the cycle)

- Initial follicle recruitment (endogenous FSH)

=> Prevent FSH levels ↓ => overcoming dominance and inducing **multi-follicular development**

- Initiation of FSH is postponed until cycle day 7 => multiple follicle development
- Higher % of monofollicular responses / starting on cycle day 2~5
- A fixed daily dose of 150 IU FSH is usually enough to induce **multiple follicular growth** when ovarian stimulation is initiated on cycle day

Conventional “long”protocols and the “mild” stimulation approach

- Conventional “long” protocol,

☐ Gonadotropins (FSH, hMG or FSH+LH) → multiple follicular development

☐ GnRH analogue → Prevent the premature LH surge (compromise the chance of retrieving oocytes)

⇒Starting in the mid-luteal phase of preceding cycle

⇒Continued until the administration of hCG

- *Initial flare of Gn release (~ 5 days) → down regulate receptors → block GnRH action on the*

Conventional “long” protocol

- Quite good predictability → Low cancellation rate → Relatively high number of pre-ovulatory follicles (of retrieved oocytes/embryos for transfer) → Satisfactory pregnancy rate
- Life-threatening, high-cost complication

⇒Ovarian hyper-stimulation syndrome (OHSS)

- Impact on a woman’ s life

⇒Weeks of **daily** injections and/or intra-nasal spraying

⇒Several blood samples and frequent ovarian echo

“mild” stimulation approach

- Patient-friendly, minimized risks, acceptable results

(a)A lower-than-usual dose gonadotropins **and/or**

Shorter duration of GnRH antagonist co-treatment

(a)Oral compounds (e.g. anti-estrogens) alone or in combination

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The key role of GnRH antagonists in "mild" stimulation regimens

- Key event to start using "mild" protocols in IVF
  (Probably not absolutely required)
- Action on pituitary release of gonadotropins:
  - Immediate suppression
  - Rapid recovery when the drug is withdrawn
- Circulating estradiol ↑ (threshold level) → Mid-cycle LH surge (requires GnRH / positive feedback loop on the pituitary)

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- At the beginning of stimulation cycle;
- Endogenous gonadotropins
- → Initiate ovarian stimulation (with a normal early follicular phase recruitment of a cohort of follicles,
- without any pituitary block

- 3 general approaches for the GnRH antagonist co-treatment in IVF

(a) Single large dose (sc): approximately the 8th day of stimulation with gonadotropins

Daily small doses

(a) Initiated on a fixed day (*fixed protocol*)

(b) Depending on the size of the dominant follicle or on estradiol levels (*flexible protocol*)

Continued → hCG for final oocyte maturation

- Administration regimens (b) and (c) are continued until the day in which hCG is given to obtain the final oocyte maturation.
- The introduction of GnRH-antagonists in the clinical IVF workout has been characterized by a long learning curve (probably still ongoing) and by several perplexities on their effectiveness
- “long” agonist protocol ⇔ daily antagonist protocol (fewer follicles & oocytes, with equivalent morphological quality, pregnancy rate ↓ 5%)

- Unfavourable *a priori* prognosis (e.g. patients with advanced reproductive age and/or with several previously failed IVF attempts)
- sub-analysis of patients with equal demographic and clinical features was performed on the same database: **similar pregnancy rates**, independent of whether GnRH agonist or antagonist had been used

- ↓ live birth rate –2.7% in the antagonist-treated group, (not statistically significant)

  (meta-analysis, 22 RCTs, 2000 ~ 2005, 3176 women)

- Significantly lower clinical and ongoing pregnancy rates in women treated with antagonists

  (Cochrane Review including 27 RCTs, 3865 patients)

IVF results in “mild” stimulation protocols vs. classical “long” protocol

- “long” GnRH-agonist regimen with relative high doses of exogenous gonadotropins ⇔ GnRH antagonists “mild” ovarian stimulation protocols with single dominant follicle selection.
- With normal/poor ovarian reserve

Women with normal ovarian reserve

- 3 prospective RCT: the effectiveness of
- “Mild” stimulation regimen ⇔ Conventional “long” GnRH agonist protocol (with an early follicular phase FSH start)

- Individually these trials found comparable results in terms of IVF effectiveness, pooling data together the ongoing pregnancy rate per started cycle sorts out to be 15% in the “mild” group and 29% in the classical group,
- A difference that suggests a well definite trend toward a lower IVF effectiveness when the “mild” strategy is applied.

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- This suggestion is further reinforced by the fact that the three RCTs did not consider freeze-thaw cycles, and the chance of obtaining surplus embryos/oocytes to freeze is obviously much **lower** in “mildly” stimulated cycles than in the classical ovarian stimulation cycles.
- Having frozen embryos/oocytes to transfer in a subsequent cycle can probably increase the overall IVF pregnancy chance per oocyte pick-up by approximately 10-15%

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- The “mild” stimulation regimen is associated with significantly lower peak estradiol levels,

⇒impact on the endometriom more softly than classical regimens

⇒The “endometrial factor” can probably represent one scored point in favour of “mild” stimulation.

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Women with poor ovarian reserve

- Overall, the published results suggest that in patients with poor ovarian reserve the choice of a mild stimulation protocol instead of a classical, high dose regimen, could be particularly indicated.
- Although these patients have a very low risk of OHSS even using high doses, the quality of both their oocytes and their endometrium could likely to be better when a smoother stimulation approach is used
- Further research, anyway, is needed to add scientific evidence to this hypothesis

Other aspects to be considered

- Risk of ovarian hyperstimulation syndrome (OHSS)
- *Risk of long term health problems*

Risk of ovarian hyperstimulation syndrome (OHSS)

- Severe OHSS is a serious and potentially life-threatening complication of IVF
- Mean incidence of 1-3% in IVF programs involving standard ovarian stimulation regimens [50].
- High risk: young, lean women with PCO => 6-9%

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- Incidence significantly lower with GnRH antagonists
- Ovulation trigger: single dose of GnRH agonist (instead on hCG) ➔ Risk of severe OHSS → ~ 0

  meta-analysis of Kolibianakis / Cochrane review by Al-Inany

  – smaller cohort of recruited follicles
  – ↓ circulating [estradiol] during ovarian stimulation
  – GnRH antagonists → Endogenous LH peak can be obtained stimulating the pituitary
- Significantly ↓ while using “mild” stimulation regimens

Heijnen /

Risk of long term health problems

- Hormones ⇔ cancer, inconclusive, (huge amount of confounders, relatively short f/u period of time)
- Although gonadotropin treatment is not considered oncogenic, nor able to significantly affect the patient's chance of having serious diseases, it appears safer to use the lowest dose possible of hormons, expecially in case of repeated IVF attempts

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Emotional stress

- Psychological burden of treatment is one of the most frequent causes of drop-out, and a significantly lower drop-out rate was observed in more patient-friendly “mild” stimulation programs
- lower incidence of minor symptoms

⇒Repeat treatment → ↑ cumulative treatment success rate and could eventually compensate for a lower pregnancy rate per cycle following “mild” stimulation

- deterioration of emotional well being/subclinical depression and/or anxiety:
  - Lower pregnancy chance per *attempt*
  - lower oocyte retrieval “per cycle” results
- No significancy

Economical costs

- lower medication consumption and with a lower cost for purchasing drugs
- A couple of studies showed the superiority of the “mild” stimulation strategy over the standard approach in terms of economical costs, especially when the “mild” strategy includes SSET
- lower costs ⇔ lower “per cycle” results

Conclusions

- Aim of rendering human IVF: successful/tolerable
- Outpatient, keep on normal life during treatment
- Still proportion of women:
  - Discomfort & emotional stress
  - Health complications (relevant or serious)
  - Very expensive
  - Limited success rate (repeated attempts)
  - Higher chance of twin pregnancy (with obstetrical & neonatal complications)

OHSS-free

- A key issue by most IVF doctors
- Further research: Ideal ovarian stimulation protocols

  ⇒High quality oocytes / optimal IVF success rates even in poor prognosis patients

  ⇒↓ undesirable effects and complications
- The “mild” stimulation philosophy

  ⇒Interesting

  ⇒True effectiveness(?)

  ⇒Impact on emotional & economical aspects(?)

Mild stimulation approach

- Selected single ET

⇒Easier, more tolerable & problem-free, cheaper

⇒Acceptable **effectiveness** on baby birth rates

⇒*Too few properly designed studies*

➔Need series of RCTs (Different subsets of patients & research groups / Involving also freeze-thaw cycles)

➔"*Mild*" stimulation protocols ⇔ Conventional GnRH agonist protocols (or GnRH antagonists) with *high gonadotropin doses*


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