Mild/minimal stimulation for in vitro fertilization: an old idea that needs to be revisited
Shvetha M. Zarek, M.D., Fertility and Sterility Vol. 95, No. 8, June 30, 2011

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Conventional *long* stimulation protocol

- GnRH agonists $\rightarrow$ suppress anterior pituitary $\rightarrow$ reproductive hormones
- Preceding menstrual cycle – mid-luteal phase $\rightarrow$ stimulation after menses
- Prevent LH surge $\rightarrow$ multi-follicular recruitment
- Side effects: formation of ovarian cysts & symptoms of estrogen deprivation (hot flushes, vaginal dryness, headaches)
- ↑dosage of gonadotropins & duration of treatment
• Dual suppression (OCP + GnRH agonist)  
  ➔ Require higher dosage of gonadotropins

• Success rates improved in the 1990s
• Improvements in IVF methodology ➔ improved implantation rates
• More high-order multiple pregnancies
• Higher incidence of OHSS
MILD STIMULATION

• Low dosage of gonadotropins (100–150 IU) started in the early follicular phase → a maximum of 10 oocytes

• **GnRH antagonist** (after 5 to 7 days of stimulation) → Prevent LH surge / prevents the LH and FSH rise by blocking the GnRH receptors
  • Immediate blockade circumvents initial surge of endogenous gonadotropins (with GnRH agonists)
  • ↓dosage & length of the exogenous Gn Tx
• GnRH antagonist  Dosages > 0.25 mg/day $\rightarrow$ ↓ implantation rates (accepted dosage for GnRH antagonists)

_Dose-finding experiments in the 1990s_

• Gonadotropins 150 IU (lower dose) $\rightarrow$ not lesser pregnancy rates (Standard dosage: 225 IU gonadotropins per day)
• Required fewer injections of analog, fewer days of stimulation, and fewer doses of gonadotropins

• Similar implantation and clinical pregnancy rates
  
  prospective randomized trials compared with the agonist

• Potential advantages: Simpler protocol, ↓ monitoring days, ↓ gonadotropin dosage, ↓ cost, ↓ negative psychological impact on infertile couples, ↓ OHSS
Hohmann et al., Prospective randomized trial

♀️ → ↓ number of oocytes → ↑ chance of conceiving

• 142 patients → group A: standard protocol, B/C: mild stimulation

B: Daily r-FSH since cycle D2 ⇔ C: since cycle D5

• A max of two embryos were transferred in all groups

• **Best graded Embryos**: A/B/C: 29%, 37%, 61%

• **Transfer rate per oocyte retrieval**: 68%, 72%, 90%

• **Pregnancy rates per embryo transfer**: similar
prospective study by Pelinck et al.

- 50 patients, mild stimulation protocol.

- **Cumulative ongoing pregnancy rate** after 3 cycles of mild stimulation: 34% (95% confidence interval [CI], 20.6–47.4%)
Heijnen et al., prospective, randomized, noninferiority trial

- 404 patients (Mild stimulation with single-embryo transfer ⇔ standard protocol with double embryo transfer)
- Cumulative pregnancy rates → term live-birth rate: 43.4% ⇔ 44.7 (Mild ⇔ standard treatment)
- Multiple pregnancy rates per couple: 0.5% ⇔ 13.1%
- days of ovarian stimulation 8.3 ⇔ 11.5
- number of injections 8.5 vs. 25.3
- Cancellation rate per started cycle 18 vs. 8.3%
Preimplantation genetic screening

• Higher stimulation conditions $\Rightarrow$ ↑mosaicism (mild stimulation can mimic the physiologic follicular response $>$ standard protocol) ............
  
  Munne et al.

• prolonged GnRH agonist standard protocol $\Rightarrow$ ↑embryo aneuploidy
Baart et al., prospective randomized trial

- Embryo aneuploidy rates
- Fluorescent in situ hybridization (FISH)
- A 9 chromosome panel
  (1,7,13,15,16,18,21,22,X,Y)
  ➔ Chromosomally normal: 55% ↔ 38%
  ➔ Fertilization rates: No differences (more oocytes were obtained in the standard group)
  ➔ Ongoing pregnancy rate: 12/35(34%) ↔ 7/31(23%)
  ➔ Interim analysis: ↓ embryo aneuploidy rate
  ➔ terminated secondary to these findings
Haaf et al.

- **↑oocytes retrieved → ↑Chromosome error rate**

- **Long protocol** (112.5–225.0 IU of FSH/day) → biopsy of 1\textsuperscript{st}/2\textsuperscript{nd} polar body → **FISH** analysis with 5 chromosome panel (13, 16, 18, 21, 22) on embryos

- **Oocytes yield**: Low(1~5), Intermediate(6 ~ 10), High(>10, oocyte aneuploidy rate 10%, > intermediate group, particularly in women < 35 y/o)

- **↓ segregation errors in early embryo cleavage states**
Verberg et al., meta-analysis, RCT

- GnRH antagonist cotreatment with a mild dosage of gonadotropins started on cycle D5
- 3 Studies, 592 cycles
- Significant ↓ retrieved oocytes \( \Rightarrow \) ongoing pregnancy rate: 15% ↔ 29%
- Embryo implantation rate 31% ↔ 29%
- Lower number of retrieved oocytes affected implantation rates
MINIMAL STIMULATION

• Yield a maximum of 5 oocytes (1~5), *Introduced in the report of Corfman et al., 1993, prospective nonrandomized study*

• Combined protocol of clomiphene citrate (CC, 100 mg orally on days 3 ~ 7) followed by a single injection of 150 IU of IM hMG on cycle day 9

→ Number of retrieved oocytes < the standard long GnRH agonist protocol (3.4 vs. 10.1)

→ No differences in pregnancy & implantation rates
• Similar findings in a larger retrospective study & many studies

• with or without adding a GnRH-antagonist to suppress the LH surge, *Williams et al.*

• Sequential CC and gonadotropin (FSH or hMG) protocol + GnRH antagonist $\rightarrow$ mean of 6.4 oocytes, *clinical PR 26%* per transfer, *Engel et al.*
• Combined protocol of CC and gonadotropin (on alternate days): 8.0 oocytes, ongoing PR 35% per started cycle, *Hwang et al.*

• More recent largest study (43,433 cycles), Japan, CC + gonadotropin: 2.2 oocytes, live-birth rate 11% per started cycle

→ PR 20% per fresh transfer ⇔ 41% by use of vitrification and cryopreserved-thawed ET, *very similar protocol* by *Zhang et al.*
Muasher Center for Fertility and IVF

• The last 2 years, with encouraging success rates

• decrease the cost and improve the patient’s tolerability and acceptance of the IVF treatment

• No patients were excluded for elevated day-3 FSH levels (under 20 mIU/mL) or age (under 44 years)
• 100 mg oral CC cycle days 3 ~ 7 → 150IU SC gonadotropin (FSH or hMG) daily since day 8 → Ganirelix acetate (Merck), 0.25 mg SC daily since morning of day 11 (with average of 3 doses)

• At least 2 follicles ≥17 mm → 10,000 IU IM Hcg

• Average of 3 visits before oocyte retrieval
  ➢ mean vials of gonadotropins: 10.5 (75 IU per vial)
  ➢ mean number of mature oocytes retrieved: 4.2
  ➢ mean number of embryos transferred: 2.4, and the
  ➢ clinical PR/cycle: 42%
Minimal stimulation protocol at The Muasheer Center for Fertility and IVF:

- **GnRH-Antag:** 0.25 mg/day
- **hCG 10,000 IU**
- **Clomiphene Citrate:** 100 mg/day
- **Gonadotropins:** 150 IU/day

Cycle Day: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Retrieval

Transfer

**TABLE 1**

Minimal stimulation protocol of clomiphene citrate, gonadotropin, and a gonadotropin-releasing hormone antagonist at the Muaasher Center for Fertility and IVF, 2008-2010.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>35.7 ± 4.4</td>
</tr>
<tr>
<td>Cancellations</td>
<td>1</td>
</tr>
<tr>
<td>Day-3 FSH (mIU/mL)</td>
<td>8.2 ± 3.8</td>
</tr>
<tr>
<td>E₂ at hCG pg/mL</td>
<td>1263 ± 802</td>
</tr>
<tr>
<td>Vials of gonadotropins</td>
<td>10.5 ± 3.2</td>
</tr>
<tr>
<td>Mature oocytes</td>
<td>4.2 ± 2.7</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>2.4 ± 0.9</td>
</tr>
<tr>
<td>Clinical pregnancy/cycle</td>
<td>42% (13/31)</td>
</tr>
<tr>
<td>Clinical pregnancy/transfer</td>
<td>43% (13/30)</td>
</tr>
</tbody>
</table>

Note: E₂ = estradiol; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin.

Minimal Stimulation for Low Responders

- No universally accepted definition for low responder
- Poor ovarian reserve (elevated D3 FSH, low antral follicle, and/or low antimullerian hormone)
- Yield of a low number of mature follicles (< 6 on a conventional IVF protocol)
- Low peak E2 level (< 900 pg/mL)
- High gonadotropin dosage (> 3,000 IU) used for the total stimulation

- Prior canceled cycles with a standard IVF protocol due to poor response
• No difference in the mean number of oocytes or the ongoing pregnancy rates

- Higher dosage of gonadotropins (6 vials) ⇔ standard dosages (2~4 vials)
  
  *Multiple studies during the early days of IVF*

- Daily 300 IU of r-FSH ⇔ 150 IU
  
  *long protocol with antral follicle count < 5, prospective randomized study, Klinkert et al./Lekamge et al.*
Systematic review and meta-analysis of 22 RCTs in low responders, *Kyrou et al.*

- Short ⇔ long (GnRH agonist protocol)
- Sequential CC/FSH/GnRH antagonist ⇔ long GnRH agonist protocol
- GnRH antagonist ⇔ short GnRH agonist protocol
- Short GnRH-agonist ⇔ natural cycle protocol
- Stop ⇔ nonstop long GnRH-agonist protocol

- No differences in PR in low responders
- No superior protocol for low responders
Prospective randomized study of low responders (basal FSH levels > 10 mIU/mL), D’Amato et al.

- Sequential protocol: CC/FSH/GnRH-antagonist ⇔ standard long GnRH-agonist protocol
  - lower cancellation rate
  - higher number of mature oocytes
  - similar clinical pregnancy and implantation rates
Muasher Center for Fertility and IVF

- Minimal stimulation protocol ⇔ standard protocol in low responders
- ↑ vials of gonadotropins
- ↓ number of mature oocytes retrieved,
- similar clinical PR per cycle initiated and per transfer
- ↓ patients were canceled
- ↓ patients without ET
Minimal stimulation versus full stimulation in low responders at the Muasher Center for Fertility and IVF, 2009–2010.

<table>
<thead>
<tr>
<th>Stimulation protocol</th>
<th>Minimal</th>
<th>Full</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>13</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>38.7 ± 3.7</td>
<td>38.9 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Day-3 FSH (mIU/mL)</td>
<td>12.1 ± 2.7</td>
<td>10.1 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>E₂ at hCG (pg/mL)</td>
<td>808 ± 353</td>
<td>1,082 ± 581</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Vials of gonadotropins</td>
<td>9.7 ± 3.3</td>
<td>49.8 ± 7.4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Days of monitoring</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mature oocytes</td>
<td>2.4 ± 1.5</td>
<td>3.8 ± 2.3</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>2.0 ± 1.1</td>
<td>2.1 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy/ cycle</td>
<td>38% (5/13)</td>
<td>36% (15/42)</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy/ transfer</td>
<td>42% (5/12)</td>
<td>47% (15/32)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Minimal Stimulation for High Responders

High responder:
• Respond to ovarian stimulation for IVF with peak E2 levels > 3,000 pg/mL, retrieval of > 15 oocytes
• very favorable prognosis for success live-birth rates
• greatly ↑ OHSS
  • usual suspects PCOS, egg donors, young women with irregular cycles, patients with a high antral follicle count (>8) for each ovary, relatively high anti-mullerian hormone level
• No detrimental effects on pregnancy and implantation rates in patients with a peak E2 level of $>3,000 \text{ pg/mL}$ ($\Leftrightarrow <3,000 \text{ pg/mL}$) and $>15$ oocytes retrieved ($\Leftrightarrow <15$)

• Severe OHSS significantly higher in high responders

• No exact data of OHSS $\Leftrightarrow$ number of oocytes retrieved & the peak E2 level
(General believed from clinical experience)

- High responders $\rightarrow$ $\uparrow\uparrow$ risk of OHSS $\rightarrow$ with the complication being almost a certainty in patients whose peak [E2] > 5,000 pg/mL and/or > 20 oocytes retrieved

$\Rightarrow$ prevention of OHSS should be the main goal in the treatment of high responders
Multiple strategies $\rightarrow$ ↓ OHSS in high responders $\rightarrow$ none of them prevent OHSS completely

- Minimal gonadotropin daily doses (100–150 IU)
- Dual suppression with oral contraceptives
- GnRH-agonist protocol
- Withdrawal of gonadotropins for 1 ~ 4 days before hCG administration (coasting)
- reducing the hCG dose (3,000–5,000 IU)
- cryopreservation of all embryos
- GnRH-antagonist protocols with a GnRH-agonist for the ovulation trigger
• In vitro maturation (IVM) of human oocytes (limited use due to inadequate experience and suboptimal pregnancy results)

• Minimal stimulation with a sequential CC/gonadotropin/GnRH antagonist protocol → offer the best strategy to ↓ or prevent OHSS for the relatively low number of oocytes retrieved
Muasher Center for Fertility and IVF

- Retrospectively, compared the stimulation characteristics and IVF outcomes

- 18 high responders with **minimal stimulation** ↔ 32 control patients with **mild stimulation protocol** (daily dose of 100–150 IU of gonadotropin) + GnRH antagonist
IVF outcome: equivalent

<table>
<thead>
<tr>
<th>Stimulation protocol</th>
<th>CO + FSH + antagonist</th>
<th>Low-dose FSH + antagonist</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nr of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>33.7 ± 3.6</td>
<td>30.6 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Day-3 FSH (mIU/ml)</td>
<td>0.6 ± 1.4</td>
<td>0.6 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>E2 at hCG (pg/mL)</td>
<td>1,600 ± 807</td>
<td>2,026 ± 942</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Viability of gonocytes</td>
<td>11.1 ± 3.1</td>
<td>19.6 ± 7.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mature oocytes</td>
<td>5.4 ± 2.7</td>
<td>8.8 ± 4.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>2.7 ± 0.7</td>
<td>2.3 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy/transfer</td>
<td>44%</td>
<td>50%</td>
<td>NS</td>
</tr>
<tr>
<td>Mean embryos frozen</td>
<td>4.6 ± 3.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

did not yield excess embryos that could be used for cryopreservation for future use.
CONCLUSION

• Success rates with IVF ↑↑over the last 30 years
  ➢ Refinement of the stimulation protocols
  ➢ Introduction of GnRH agonists/antagonists
  ➢ Improvements in IVF culture conditions
  ➢ Extension of the transfer to day 5
  ➢ Gentle transfer techniques under ultrasonography
  ➢ Preimplantation genetic diagnosis with transfer of euploid
• Costly, stressful (due to multiple office visits, injections, blood drawings, ultrasound examination)

• ↑ risks of multiple pregnancy and OHSS

😊 Most common cause of dropout from IVF: Physical and/or psychological burden of treatment

(In the United States, ↓ IVF rates ⇔ lack of insurance coverage / ↓ median income)
Opinion of this article

• Minimal stimulation:

 ✓ ↓ the total cost of medications (savings of > $3,000)

 ✓ ↓ stress of treatment (average of 3 ⇔ 6 visits)

 ✓ ↓ number of injections, blood drawings, ultrasound

 ✓ ↓ the incidence of OHSS (underreported → not enough attention to ↓ incidence in high-risk patients)
Advantages/disadvantages/resistance of mild stimulation protocol over the last 10 years, Fauser et al.

Disadvantages:
• ↓ potential to obtain excess oocytes for cryopreservation
• ↓ ability to transfer 1 or 2 blastocysts (due to the lower number of embryos)
• ↓ the number of oocytes from egg donors that can be used to 1 or 2 recipients

Preimplantation genetic diagnosis ⇔ Sizable number of patients elect not to cryopreserve excess embryos for multiple reasons
During the last 10 years... **Mild/minimal stimulation**

- ↓ High-order (≥ triplet) multiple pregnancy in US
- An attractive option for patients with OHSS in a previous cycle/↓ OHSS in high-responder patients
- May not be the optimal treatment protocol
- Can be an option for many patients (not costly, stressful process that involves multiple daily injections for a lengthy period of time with increased complications)
THANK YOU FOR LISTENING