

Mild/minimal stimulation for in vitro fertilization: an old idea that needs to be revisited

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Conventional *long* stimulation protocol

- GnRH agonists → suppress anterior pituitary → reproductive hormones
- Preceding menstrual cycle – mid-luteal phase → stimulation after menses
- Prevent LH surge → 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 \downarrow 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 → ↑mosaicism
(mild stimulation can mimic the physiologic
follicular response > standard protocol)
Munne et al.
- prolonged GnRH agonist standard protocol → ↑
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 1st/2nd 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 → 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 → 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.*

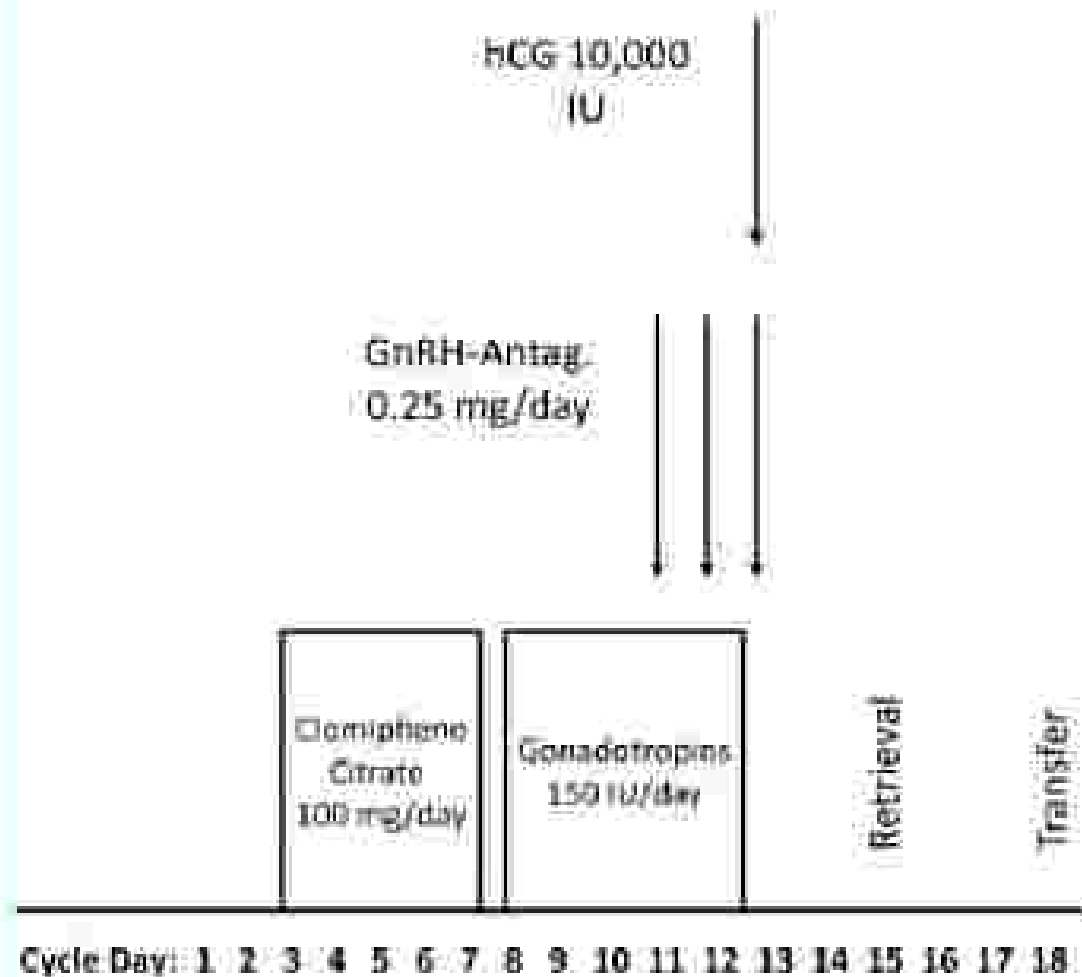
Muasher Center for Fertility and IVF

- 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%

FIGURE 1

Minimal stimulation protocol at The Musher Center for Fertility and IVF.



Zarek. *Minimal stimulation for IVF.* Fertil Steril 2011.

TABLE 1

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

No. of patients	31
Age (y)	35.7 ± 4.4
Cancellations	1
Day-3 FSH (mIU/mL)	8.2 ± 3.8
E ₂ at hCG (pg/mL)	1283 ± 802
Vials of gonadotropins	10.5 ± 3.2
Mature oocytes	4.2 ± 2.7
Embryos transferred	2.4 ± 0.9
Clinical pregnancy/cycle	42% (13/31)
Clinical pregnancy/transfer	43% (13/30)

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

Source: Minimal stimulation for IVF. *Fertil Steril* 2011.

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
- One or more

- 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 \Leftrightarrow standard protocol in low responders
 - \uparrow vials of gonadotropins
 - \downarrow number of mature oocytes retrieved,
 - similar clinical PR per cycle initiated and per transfer
 - \downarrow patients were canceled
 - \downarrow patients without ET

Minimal stimulation versus full stimulation in low responders at the Muasher Center for Fertility and IVF, 2009–2010.

	Stimulation protocol		P value
	Minimal	Full	
No. of patients	13	42	
Age (y)	38.7 ± 3.7	38.9 ± 2.9	NS
Day-3 FSH (mIU/mL)	12.1 ± 2.7	10.1 ± 3.7	NS
E ₂ at hCG (pg/mL)	808 ± 353	1,082 ± 581	< .05
Vials of gonadotropins	9.7 ± 3.3	49.8 ± 7.4	< .01
Days of monitoring	3	6	
Mature oocytes	2.4 ± 1.5	3.8 ± 2.3	< .05
Embryos transferred	2.0 ± 1.1	2.1 ± 1.2	NS
Clinical pregnancy/ cycle	38% (5/13)	36% (15/42)	NS
Clinical pregnancy/ transfer	42% (5/12)	47% (15/32) ^a	NS

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 \uparrow 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 $>3,000$ pg/mL ($\Leftrightarrow <3,000$ 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 → ↑↑ risk of OHSS → with the complication being almost a certainty in patients whose peak [E2] > 5,000 pg/mL and/or > 20 oocytes retrieved

→ prevention of OHSS should be the main goal in the treatment of high responders

Multiple strategies → ↓ OHSS in high responders → 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

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- 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

Minimal stimulation versus full stimulation in high responders at the Musher Center for Fertility and IVF, 2009–2010.

IVF outcome: equivalent

Stimulation protocol

CO + FSH + antagonist

Low-dose FSH + antagonist

P value

No. of patients

n

n

Age (y)

35.7 ± 3.8

30.8 ± 3.5

NS

Day-3 FSH (mIU/mL)

6.0 ± 1.4

6.8 ± 1.6

NS

E₂ at HCG (pg/mL)

1,500 ± 807

2,028 ± 942

<.05

MB's of gonadotropins

11.1 ± 3

<

19.6 ± 7.3

<.05

Mature oocytes

5.4 ± 2.7

8.8 ± 4.0

<.05

Embryos transferred

2.7 ± 0.7

2.3 ± 0.7

NS

Clinical pregnancy/transfer

44%

50%

NS

Cycles with freezing

did not yield excess embryos

20%

Mean embryos frozen

that could be used for

4.8 ± 6.1

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 (\geq 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